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THE PRESENT DAY TREATMENT OF MALARIA*

A. J. WALKER, M. D.
NEW ORLEANS

In the vast majority of cases, if the patient's symptoms are due to malaria, the parasite can be demonstrated in an adequately stained thick blood film. In highly endemic areas, possibly one patient in two hundred will be encountered in which the acute symptoms will demand immediate treatment even before a blood examination can be made. Efforts to make a diagnosis should be continued even after treatment has begun. "Fever with negative smears should be studied, not treated. There is no need to hurry."[1] At the same time, a careful physical examination may reveal the presence of a pneumonia, meningitis or other condition which makes the malaria infection one of secondary importance.

Falciparum malaria can be fatal but it is also more readily cured. Some forms of malaria show great tendency to relapse while other infections are, at times, self limited.

Specific treatment includes: (1) management of the presenting attack; (2) eradication of the infection if possible; (3) suppression of further clinical manifestations; (4) prevention of new infections developing to clinical proportions.

If one analyzes the situation of a patient in whose blood the finding of some thirty definite parasites has permitted a diagnosis of vivax malaria to be made, we are struck by the fact that, aside from knowing the existence of the infection and its specific name, we know extraordinarily little. There are three variables on which the course of the disease and the success of any form of treatment depend:

Species strain variations	*Drug* varied behavior	*Individual* resistance susceptibility suppression

Because of these variables, the League of Nations Commission, in 1933, was unable to recommend any standard form of treatment.[10] Such variables also explain why a treatment method seemingly highly effective in one region may prove quite disappointing with the same species in a different part of the world. Examples: varying relapse rates in vivax infections; a few atabrine-resistant strains of falciparum on Wewak.[2]

The place which quinine has occupied in malaria therapy for over a century has now been preempted by atabrine and other synthetic compounds known to be definitely superior to quinine when administered in adequate dosages. This time-honored and expensive drug is, therefore, relegated to the position of adjuvant to certain other substances.

Over the years, the scheme of dosage for quinine was developed empirically and that used for the individual attack is essentially the same as used thirty years ago. At the

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time plasmochin was developed, in 1926, the medical world was quite ready to try out other compounds. Unfortunately, this very excellent antimalaria drug was found to be toxic in certain instances and its use came to be limited to its gametocidal action. In a few years the profession became extremely cautious of it. This caution was carried over to all other synthetic drugs and actually hindered a really thorough clinical trial of the next synthetic to appear in 1930—atabrine.

Still working somewhat empirically in regard to dosage, atabrine was given in as small doses as possible. The original treatment was 0.1 gm. thrice daily for five days, later increased to seven days. Even on a five day treatment some patients became yellow, since atabrine is a yellow acridine dye with predilection for the skin. This yellow color suggested to the laity and too often to the physician—jaundice—and therefore liver damage, neither of which was present nor can be produced by atabrine. Furthermore, it was noted, quite correctly, that atabrine did not seem to bring about clinical improvement as quickly as did quinine.

Before further new drugs against malaria were forthcoming, the era of the sulfa group of drugs arrived. The early recognition that their efficacy depended upon adequate blood concentrations soon led to comparatively simple methods of determination of sulfa blood levels. It was not long before the same principles were applied to atabrine. During experiments which showed that the fears of atabrine toxicity were groundless, it was also seen that adequate blood concentrations were not obtained with the old regime until about the fifth day.[3] Ninety per cent of the atabrine is fixed in the tissues before the blood concentration begins to build up. Quinine, on the other hand, is rapidly absorbed and its maximum concentration is reached in four hours. When the obvious was tried, namely to "load" the atabrine dosage in the first 24 hours, it was soon apparent that atabrine was equally or more effective than quinine and the required dosage was readily tolerated. The feared toxicity had proved to be a myth born of skepticism and conservatism.

In 1939, the Germans patented a drug called "sontochin" which, for some reason, was not given an adequate clinical trial until brought to America in 1942. Another drug of this same series was "resochin" or what we know as chloroquine.[5] This white substance has roughly the same therapeutic properties as atabrine, is effective in fewer doses and does not have the objectionable yellow color.

Quinine and its equivalent-totaquine, atabrine and chloroquine complete the list of those drugs which have proved to be effective in removing the asexual forms of the parasite from the blood and relieving the clinical symptoms. Since they are capable of doing only this, the futility of long continued treatment was soon evident. Moreover, after cessation of these drugs given suppressively, further clinical activity occurred. One very important finding from the investigations of effects of atabrine suppressive therapy came to light.[4] If continued for 23 days after the infective bite, falciparum infections could be acquired, could reach demonstrable, if not clinical proportions and be completely eradicated. Hence the practice of continuing one tablet of atabrine daily for three weeks following a therapeutic course of treatment.

The large scale experiments on human volunteers in Austrilia, which resulted in the demonstration of the ability of atabrine to eradicate falciparum infections while vivax infections were merely suppressed, also confirmed previous observations. The patient's blood, when transfused into other individuals, is not infective between 30 minutes after the bite and sixth to eighth day. This is excellent evidence to suggest the existence in man of an exo-erythrocytic stage similar to that observed in various species of bird malaria.

When the supplies of quinine were threatened, thousands of compounds were tested for anti-malaria activity against bird malarias. Those which showed promise were then tried out against human species

of malaria. The drugs mentioned so far all appeared to attack the younger asexual forms of the parasite or the gametocytes. One which seemed to affect the exo-erythrocytic stages of bird malaria more than others was paludrine. This drug seemed to attack the dividing forms of the human parasites as well.[6, 7, 8] Preliminary reports first appeared in 1945.[9] Given for 10 days it will eradicate falciparum infections while relatively small single doses will control the attacks of either vivax or falciparum.

If given during the incubation period, when parasites are not yet present in the peripheral blood, paludrine evidently attacks the dividing forms of the pre-erythrocytic stages. Single doses, given during this period will completely suppress all falciparum infections and a high percentage of vivax as well.[6] It is thus a true prophylactic as well as a therapeutic drug. Much work remains to be done in investigating this most promising compound.

The problem of the relapsing type of vivax remains. This has received so much publicity that its importance has been somewhat exaggerated. The Navy's figures for 10,000 cases from the Pacific area reveal that: 61 per cent had one relapse; 27 per cent had two relapses; 9 per cent had three relapses; 2 per cent had four or more.

These persistent relapsers are a problem to themselves as well as to their physician. A very careful history usually reveals sojourn in New Guinea, Guadalcanal, Leyte or Luzon, frequently with long periods of adequate atabrine supression. One or more attacks may have taken place overseas or may have been delayed for months after return to the U. S., even a year or more after atabrine has been discontinued.

In many instances, self-treatment with inadequate amounts of atabrine or quinine for one to three days has resulted in an individual attack being continued over several weeks. Each febrile incident was counted as an "attack" which might result in a formidable total. One patient complained he had suffered 45 attacks which careful analysis reduced to 14. Such a history may frequently reveal a surprisingly regular periodicity of relapse which may be very useful in anticipating further attacks.

It is important that these cases receive an adequate amount of therapy for each episode, as approximately 50 per cent are terminated. Frequent blood examinations for the slightest symptoms, especially during the expected period, will allow treatment to be initiated before symptoms become severe. Where the attacks are frequent and at short intervals it may be well to try a combination of quinine and plasmochin for 10 to 14 days. If available, a further new drug—pentaquine—has been shown to be most effective in the cure of relapsing vivax infections. It must be administered every four to six hours day and night for 14 days together with 0.3 gm. of quinine.[10] Since this tedious treatment will only be practical in a limited number of cases, preferably hospitalized patients, it seems these individuals would best be served by early prompt anticipatory blood examinations and treatment with chloroquine or a continuous and indefinite suppression with chloroquine or paludrine by unit doses once weekly.

Herewith is appended in tabular form a summary of the important information relating to the six drugs already mentioned.

QUININE AND THE CINCHONA ALKALOIDS

There are several salts of quinine: sulphate, bisulphate, dihydrochloride, bromate, tannate, and so on. Totaquine contains 70 per cent of all the crystalline alkaloids of the cinchona bark, quinine, quinidine, cinchonine and cinchonidine. Totaquine U.S.P. is used orally in the same dosage as quinine.

Quinine is readily absorbed and a peak plasma concentration is reached within four hours but it is equally rapidly excreted. The efficient blood level of 3 to 5 mgm. rising to 10 mgm. per liter should be maintained for several days.[12] Quinine sulphate or dihydrochloride 1.0 gm. (15 gr.) in capsule or tablet form is given every six hours for three doses and then 0.6 gm. (10 gr.) three times daily for a total of seven and sometimes ten days. Quinine should not be used

TREATMENT OF MALARIA INFECTIONS

"Any person, irrespective of the presenting symptoms or absence of same, who has lived in or merely passed through an endemic area, should be considered to have malaria until proven to the contrary."[11]

The immediate attack = primary or relapse.

The underlying infection = falciparum malaria can be eradicated by atabrine, chloroquine and paludrine over maximum period indicated below.

vivax (and quartan) malaria may relapse; 50+% may be cured by adequate treatment of first attack.

DRUG	QUININE	PLASMOCHIN	PENTAQUINE SN 13,276	ATABRINE	CHLOROQUINE SN 7,618	PALUDRINE M-4888 SN 12,837
Dose	0.6-1.0 gm.	0.010 gm with quin. after At.	0.010 gm. +quin. 0.3	0.100 gm.	0.500 gm.	0.100 gm.
Frequency	t. i. d.	t. i. d.	q. 4-6 hrs.	t. i. d. after first 24-48 hrs.	u. i. d. after first day	b. i. d.
Duration (days)	7-10	5-14	14	7	3-4	1-14
Bl. level	3-10 mgm. L.	?	?	40-100 y per L.	100-160 y per L.	25-150 y per L.
Toxicity	nil side effects	yes	⅛—½ of plasmochin	nil; yellow color	nil: rare side effects	nil
Falciparum infection	controls	cures	cures	cures	cures	cures
Vivax relapses	early	decreased	80+% cures	delayed	delayed	less delayed
Suppressive dosage	0.6 gm. daily	—	—	0.1 gm. daily	0.25 gm. weekly	0.1 gm. weekly

in areas where blackwater fever is known to occur. Ampules of various salts of quinine are available, usually in amounts of 0.5 and 1.0 gm. in 5 to 20 c.c. of solution, for parenteral use.

Plasmochin (plasmoquine, pamaquine U. S. P., pamaquin B. P., aminoquin, plasmochin naphthoate), is n-diethylaminoisoamyl-8-amino-6-methoxyl quinoline naphthoate. This, the first of the synthetic antimalarial drugs; stopped schizogony and cured the clinical attacks of vivax and quartan malaria but gave indifferent results with falciparum. It did, however, sterilize the gametocytes, especially the more resistant falciparum gametocytes. In high doses it even neutralized sporozoites but these dosages were too toxic. Used in doses of 0.01 gm. three times daily for five days during the last five days of quinine therapy or beginning three days after atabrine therapy has been stopped, gametocytes are eliminated and in some areas seems to have had some effect in reducing the number of relapses. More recently, quinine and plasmochin have been used together for 14 days in the treatment of persistent relapsing vivax infections. Atabrine tends to augment the toxicity of plasmochin and the two should never be given simultaneously. At the first sign of epigastric pain, blueness of the lips and shortness of breath, plasmochin should be discontinued. Excessive dosage produces hemoglobinuria.

Pentaquine (SN 13,276) is 6-methyoxy-8-(5-isopropyl amino amylamino) quinoline monophosphate, a yellowish crystalline substance moderately soluble in water. Rapidly absorbed and rapidly excreted, the administration is at frequent intervals day and night and its effect is enhanced by the simultaneous ingestion of quinine. It is said to be one-third to one-half as toxic as plasmochin and is thus unsuitable for unsupervised treatment or for suppression but gives a high proportion of cures in relapsing vivax malaria. Tablets of 0.01 to 0.025 gm. are given together with 0.3 gm.

quinine every four hours for 14 days.

Atabrine (atabrin, atebrin, chinacrin dihydrochloride, quinacrine U. S. P., mepacrine B. P., metoquina, etc.) is 3-chloro-7-methoxy-9-(1-methyl-4-diethylamino) acridine dihydrochloride, a bitter, bright yellow dye. Since the tissues must first be saturated by the drug the plasma level rises slowly until an effective level of approximately 30 micromilligrams per liter is reached. Two 0.1 gm. tablets are given every four to six hours for the first 24 to 36 hours, then one tablet three times daily for a total of seven days when approximately 3.0 gm. have been ingested. In falciparum infections, one tablet is continued for a further 21 days. Atabrine dihydrochloride 0.2 gm. in ampules is available for parenteral administration. This amount, dissolved in 5 to 7 c.c. of sterile distilled water, is injected intramuscularly every six to eight hours until the severe symptoms have abated or oral administration is tolerated. Two-tenths gram of atabrine in 10 c.c. of distilled water or added to infusions of larger volume up to 500 c.c. are given very slowly intravenously. The unfavorable reactions to intravenous atabrine which have been reported were usually with other preparations of the drug or with doses much higher than stated here.

Where nausea and vomiting are present or threaten, when the patient is acutely ill, parenteral atabrine or quinine should be used promptly. In dangerous falciparum infections, especially where there are signs of shock or cerebral involvement, one should not hesitate to give the drugs intravenously.

Chloroquine (resochin, sontochin, aralen) is 7-chloro-4-(4-diethylaminp-1-methylbu-is 7-chloro-4 (4 diethylamino-1-methylbutylamino) quinoline diphosphate, a white crystalline powder. It has the same therapeutic properties as atabrine,[15] but acts more quickly with fewer doses and has no objectionable color. Parasites disappear from the blood very quickly. The blood plasma level of 50-200 micromilligrams per liter is obtained during therapy.[14] Four 0.25 gm. tablets given on diagnosis, two tablets six hours later and then two similar tablets each morning for two or at most three successive days, constitute the entire treatment for an individual attack.

Paludrine (SN 12,837, M-4888) is N1-p-chlorophenyl-N5-isoprpyl biguanide acetate, a somewhat soluble white powder.[13] In contrast to the preceding drugs, paludrine appears to have some direct effect on the non-erythrocytic forms of malaria parasite as well as the asexual symptom-producing stages. It has been shown to be a complete causal prophylactic in falciparum malaria.[6] The blood level varies with the dosage used from 25-1200 micromilligrams, the concentration in whole blood being about four times that of plasma. Paludrine is rapidly absorbed with maximum levels obtained in four hours, falling off in 12 hours with increasing levels if taken twice daily. Tablets of 0.100 gm. are available and while single doses of 0.050 gm. to 0.300 gm. have controlled individual attacks, one tablet thrice daily for 10 days or twice daily for 14 days is advised for the eradication of falciparum malaria. Chronic relapsing vivax malaria is not cured but one tablet every five to seven days is sufficient to abolish symptoms and may contribute to an ultimate cure.

SYMPTOMATIC TREATMENT

In addition to the specific treatment, supportive treatment and good nursing care will do much to lessen the severe discomfort of the malaria attack. The individual vivax paroxysm may be much more severe than one due to falciparum. Bed rest, abundant fluids with glucose and fruit juices may be given while additional sodium chloride may be required. For the first two days, 1.0 gm. of sodium bicarbonate may well accompany each dose of quinine or atebrine. Purgation only increases the patient's discomfort so an enema should be given if required. An electric pad if available or hot water bottles are more effective than blankets during the chill period. Frequent changes of bed and body clothing are necessary and appreciated. The diet should be as generous as the patient can take. Post-treatment with ferrous sulphate 0.6 gm. thrice daily may well be given if

any degree of anemia has resulted.

PROPHYLAXIS AND SUPPRESSIVE MEDICATION

Many years ago, the daily taking of 5 grains of quinine was found to reduce appreciably the amount of malaria among non-immune people in some of the most unhealthy parts of India and Africa. Later it was seen this amount was inadequate and the daily dose was increased to 10 grains. Neither quinine, atabrine nor chloroquine are prophylactics in that they prevent the infection developing. They merely, when taken regularly, keep the infection below clinical levels, hence the term suppression. When this form of medication is discontinued clinical activity, particularly of vivax infections, may occur. Delayed primary attacks have appeared from 30 days to 18 months after discontinuance of suppressive quinine and atabrine. Thus, suppression is a matter of expediency rather than a sound method of malaria control. Atabrine and chloroquine are more efficient than quinine as suppressives in that falciparum infections may be acquired and eradicated without ever developing to clinical levels.[4]

Paludrine, in addition to acting as a suppressive if taken from the second to fifth day of a known sporozoite inoculation, can stop all falciparum and some vivax infections in the non-erythrocytic stage. It is, thus, a true causal prophylactic.

Plasmochin and pentaquine are too toxic for continued use as suppressives.

The efficient dose of each of the other drugs and the frequency of their administration is shown in the table. Persons showing an idiosyncrasy to any two of the above drugs should not be permitted to go to any area of high malaria endemicity.

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DISCUSSION

Question: Dr. Walker, is this pentaquine quite toxic?

Dr. Walker: It is apparently a third to a half as toxic as plasmochin.

Question: How toxic have you found plasmochin?

Dr. Walker: In our experience we have not very often found toxic effects but when they occur they have been quite severe. I feel if people are going to have toxic reactions with plasmochin they may have reactions to pentaquine as well.

Question: How long do you keep up chloroquine?

Dr. Walker: We treat the individual attack as suggested here. The first day we give one gram, four tablets, on diagnosis, and six hours later two tablets and then on three successive mornings—two tablets. The mimeograph form is not quite complete on that. That is the complete treatment until the next attack.

Question: You do not keep up suppressive treatment?

Dr. Walker: No, unless relapse is too frequent. I have a young man going to school at Tulane. He worries about his examinations and does not want an attack to cause him to miss any of them. He does not like to take a chance so we give him paludrine every five days; one tablet, or he could take chloroquine. The best way is to treat the attack and then wait for the next attack.

Question: Routinely, you do not advise once a week?

Dr. Walker: No. If a patient is having attacks under two months and he has a good many and is

tired of them, all well and good, give chloroquine suppressively for three to six months. As some patients are likely to drop out after each treatment, how are you going to find out if the infection is worked out and finished when you keep up suppression on them all the time. We are seeing this year one-third or one-quarter as many patients as we saw last year. These Pacific cases are running out at a tremendous rate. My own opinion is that after three years they will be extremely rare. If the attacks are frequent and troublesome and you cannot anticipate because they do not show any regular periodicity, examine the blood at frequent intervals. The patient should not have to go to bed with the attack. Several have not been in bed for some time. I may say about paludrine that it seems to be a tremendously effective drug. It is obviously a drug for suppression and very small doses will control an individual attack. We are using 300 mg. temporarily but actually 100 or 150 mg. have been given with apparently no increase in relapse. The sheet there indicates the suppressive treatment—one paludrine tablet every seven days. There is no rule of treatment. The individual case should be treated according to its behavior. Paludrine should be available in the New York market very shortly. It is available in England at the present time. Chloroquine has been on the open market since October. The great advantage of chloroquine is the total treatment time is four days and people who are over their symptoms universally are neglectful of further medication so that my own opinion at the moment is that paludrine will be the drug of suppression and chloroquine the drug of treatment.

Question: Have you had any failures with atabrine in cases that responded to other drugs like chloroquine?

Dr. Walker: I have not had failures with atabrine where doses have been adequate. There are failures with insufficient doses; the attacks merely interrupted, not checked.

Question: I had one patient in the hospital who did not respond and gave chloroquine and he responded.

Dr. Walker: It is dramatic how quickly chloroquine clears the blood of parasites. Paludrine does not behave that way. It seems to attack parasites in segmenting stage and they are then found in this stage for two, four or six days.

Question: What about the effect of the drug on quartan type? We are not free of this in our community but hope we might be.

Dr. Walker: As you know we do not have sporozoite induced quartan at the present time but the needle induced quartan behaves clinically the same and reacts to the drugs identically as does vivax. Quartan is perhaps a little slower to be cleared from the blood with chloroquine but it is cured in the same way as vivax. It is not necessary to give more than a single dose of paludrine for treatment of needle induced vivax or quartan infections.

ENTERIC INFECTION OR INFESTATION SINE DYSENTERY*

DANIEL N. SILVERMAN, M. D.
AND
ALAN LESLIE, M. D.
NEW ORLEANS

Since biblical times dysentery has been recognized as one of the common diseases. Until recently diarrhea has been considered a symptom essential to the diagnosis. The identification of *E. histolytica* by Loesch in 1875 and of *B. dysenteriae* by Shiga and Kruse in 1897 did not change this thought although these discoveries helped enormously to clarify the subject of the diarrheal diseases. Acute dysentery with its typical clinical picture has never posed a diagnostic problem, nor has chronic dysentery, when characterized by irritative bowel manifestations of lesser severity but greater duration than the acute disease. In this presentation there will be considered a less generally appreciated type of chronic dysentery with symptoms different from those of the typical diarrheal group.

Although the word "dysentery" has been loosely applied to diarrheas generally, it has been limited by medical definition to disease caused either by *E. histolytica* or by a member of the Shigella group. In 1945 Silverman and Leslie[1] presented the first of a series of cases of chronic Salmonella infection clinically indistinguishable from the chronic cases of "dysentery tardive" under discussion. These cases of chronic Salmonella infection have been shown[2] to constitute a formidable group, and so are being included here.

During the past three years 123 unselected private cases of proved enteric infection or infestation were studied. For several reasons these do not represent a fair sampling of the general run of the dysenteries. First, it must be remembered that acute bacillary dysentery is a self-limited disease except for the 15 to 20 per cent of cases which become chronic, and is normally han-

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dled by the family physician, not by the gastroenterologic consultant. Second, previously proved cases of enteric infection or infestation seen by the gastroenterologist are usually those which have not responded favorably to methods of therapy available to the general practitioner, and have become chronic, or those which have been low grade and chronic from the outset. In addition, the gastroenterologist sees patients with abdominal complaints of more or less obscure nature, a fair proportion of whom will prove to have specific enteric disease.

The group of cases which comprises the substance of this paper is an important one, not only in the South but over the entire country. It is safe to assume that where there is acute dysentery, chronic dysentery is likely to occur. This is well appreciated in the South, but is perhaps less so in other parts of the country, where such relatively minor abdominal complaints as lead Southern physicians to suspect the presence of dysentery are not generally associated with the possibility of enteric infection or infestation. It is well known that acute dysentery occurs commonly in the more temperate as well as in the subtropical areas of the United States. Local outbreaks have been reported in Washington, Illinois, Michigan, New York, Canada, and other Northern as well as Southern localities.[3-7] Since the specific organisms have been shown to thrive in Northern as well as Southern environment, chronic dysentery is probably prevalent over our entire country. An increasingly important cause of the dissemination of this disease in the United States is the apparent relaxation of quarantine regulations, and, with the expansion of travel facilities, both air and sea, the swelling influx of our good neighbors to the south.

Chronic dysentery and the carrier state are endemic in Latin America and, as foreseen by Silverman[8] in 1926, have become so in the United States. Figures vary, but it has been conservatively estimated[9] that the *E. histolytica* is harbored by 5 to 10 per cent of the population of the United States and by a much higher percentage of the peoples of Latin America. It is perfectly obvious, however, that clinical amebiasis occurs in far smaller percentages. On the other hand, it must be apparent that minor complaints of indigestion, deemed hardly worthy of a doctor's attention unless recurrent and disturbing, may result from potentially serious enteric disease. What is becoming generally known about chronic amebic disease of the colon must be equally true of chronic bacterial disease, since in the present series of 123 unselected cases there was no diagnostic differentiation on the basis of symptomatology among the cases of amebic, Shigella, or Salmonella disease. Physical and proctoscopic examination only occasionally aided this differentiation, the diagnosis being established by laboratory examination and confirmed by response to therapy.

Here we are not dealing with obvious disease with the easily visible diffuse mucosal inflammation of bacterial infection or with the discrete undermined ulcers of amebiasis. These chronic cases, especially the ones without diarrhea, may have a pathology no more extensive than a few scattered lesions in the cecum and ascending colon, always, however, with the Damocleian threat of rapid dissemination. It is easy to see how this type of pathology may give rise to less typical symptoms or be referred to a remote location, in or out of the gastrointestinal tract.

Table 1 illustrates the type and frequency of symptoms seen in these cases. No statistically significant differences can be drawn to associate particular symptoms with specific organisms. What is of principal clinical significance is the absence of any history of diarrhea in 43 cases and the existence of actual constipation in 24 cases. Diarrhea as a chief complaint was noted in only 13 cases, although 20 gave a history of severe acute diarrhea in the past. Thirty-nine patients reported occasional or recurrent diarrhea. Epigastric pain occurred in 20 patients, and in some was associated with other so-called gastric symptoms. Melena occurred in 16 of the cases of amebiasis but in only eight of the cases of bacterial

TABLE 1

	E. Histolyt.	Flexner	Shiga	Duval-Sonne	Para A.	Para B.	Total
Diarrhea as chief complaint	3	4	0	2	1	3	13
Past history of acute diarrhea	9	5	0	1	1	4	20
History of recurrent or occasional diarrhea	12	14	5	0	2	6	39
No history of diarrhea	20	10	4	5	1	4	44
Constipation	9	6	4	5	0	0	24
Abdominal pain; diarrhea	10	6	2	2	1	6	27
Abdominal pain; no diarrhea	17	11	5	4	1	6	44
Epigastric pain	13	6	4	3	0	3	29
Nausea	5	2	3	1	3	3	17
Pyrosis	9	1	0	1	1	1	13
Melena	16	4	1	1	0	2	24
Fever	1	4	0	1	1	3	10
Weight loss	4	5	4	1	0	6	20
Lassitude	3	3	2	0	1	2	11
Miscellaneous (headache, backache, flatulence, arthritis, neuralgia, dysmenorrhea)	17	7	2	1	1	4	32
Number of cases	51	33	9	8	5	17	123

disease. The less specific symptoms appeared about uniformly among all the groups, and it was not possible to demonstrate that there was any greater incidence of complaints in any single group.

Particular attention is directed to the cases of chronic Salmonella infection. From the table it is seen that there is nothing characteristic to distinguish these cases from the true dysenteries. Within the limits of the number of cases presented, the minor percentage differences cannot be considered significant, whereas the over-all similarities are apparent.

In considering therapy and the results thereof, sharp distinction must be made between protozoon and bacterial disease. The cases of amebiasis were given specific treatment, usually emetine plus diodoquin or carbarsone. Following three or four weeks of therapy, with few exceptions, cure was obtained, and confirmed by repeated subsequent examinations. The sulfonamides having been found to be of little or no value in the management of chronic cases of intestinal infection, we are still faced by the lack of specific therapeutic agents. Therefore, these cases received, in addition to aggressive supportive therapy, extended courses of autogenous vaccine desensitization. The results of treatment over periods of several months to two years have been generally satisfactory, although the definite end-point of cure as seen in amebiasis has not been observed. Anti-amebic therapy caused rapid regression and disappearance of the colonic lesions which were within view of the sigmoidoscope. On the other hand, disappearance of signs of bacterial disease, such as ulceration, mucosal hyperemia, vasodilatation, submucosal lymphatic hypertrophy, and the presence of excess mucus was slow. The sigmoidoscopic signs and progress were identical in both Shigella and Salmonella disease. Some of these cases, although subjectively improved after long continued treatment, continued to harbor the organism and showed little or no improvement in the bowel. Some observers, particularly Felsen,[10] would incline to classify these as cases of ulcerative colitis, caused by specific organisms, but evidence for this contention is not convincing.

DISCUSSION

The observations made do not apply to acute dysentery, which constitutes the large

majority of clinically recognized cases of infection or infestation of the bowel, but to the less generally appreciated but equally important cases of chronic dysentery. The importance of the chronic type of the disease stems not only from the diagnostic standpoint but from the public health consideration as well, since epidemics can and almost certainly have originated from such cases which have escaped detection.

The absence of irritative bowel symptoms or a history thereof does not negate the possibility of specific enteric disease. A history of sporadic loose bowels, perhaps only in the distant past, is helpful to direct attention to the bowel as a possible site of present disease, but even this history may not be educible. In this connection it is well to remember that it is frequently difficult to obtain bacteriologic proof of infection. Repeated culture of bowel scrapings obtained proctosigmoidoscopically may be necessary before a positive culture is reported. In the face of often frank pathology, the reason for this is not clear.

In considering the bowel pathology visible on endoscopic examination, it may suffice to state that in chronic bacterial dysentery there is variation from a practically normal appearance to one of severe inflammation with diffuse redness, vascular engorgement, mucosal edema and ulceration, and areas of submucosal lymphatic hypertrophy. Cases of amebiasis, similarly, may present no apparent abnormality or may show anything from minor to extensive ulcerative involvement. Roentgenographic examination of the colon may show no abnormality or may show local or diffuse irritability, but not the changes seen in chronic ulcerative colitis, unless this disease coexists, as it did in two of the cases presented. X-ray study of the small intestine frequently shows the pattern described by Golden[11] as occurring in secondary deficiency states, and by Silverman and Leslie[1] as occurring in chronic Salmonella infection.

The inclusion of cases of Salmonella infection in a discussion of dysentery may seem open to dispute. But these cases presented no feature which could serve to distinguish them from the cases of chronic *B. dysenteriae* infection, clinically, sigmoidoscopically, or radiologically; only the bacteriologic differentiation obtained. They bore even less similarity to paratyphoid fever than the cases of chronic dysentery did to acute dysentery.

It is therefore submitted that the definition of dysentery should be broadened to include such cases of chronic Salmonella infection as satisfying the stated clinical, proctoscopic and radiologic criteria.

SUMMARY

1. Clinical, bacteriologic, radiologic, pathologic, and epidemiologic considerations in 123 unselected private cases of chronic enteric disease caused by *E. histolytica*, *B. dysenteriae*, and *B. paratyphosus* are presented, the frequent insignificance of diarrhea in the history being emphasized.

2. Since chronic Shigella and Salmonella enteric infection can only be differentiated bacteriologically, a brief is made for the incorporation of the latter into the dysenteries, and broadening the definition of dysentery to include the Salmonella as an etiologic agent is suggested.

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EXTRA-INTESTINAL AMEBIASIS*

WALTON R. AKENHEAD, M. D.†

NEW ORLEANS

Amebiasis and its complications are problems of considerable incidence and importance which may perhaps become increasingly so with the return of so many individuals from areas more endemic than our own. Several excellent papers on various aspects of the subject have appeared during the past few years, but repetition and attention are perhaps justified in an attempt to provoke and maintain a high index of suspicion in a condition in which diagnosis is all the more important since definite specific therapy is available.

Endameba histolytica is estimated to exist in the intestinal tract of from 5 to 20 per cent of the general population[1, 2] and is capable of invading from this primary focus practically all of the organs and tissues of the body. The liver, lungs and pleura are relatively common sites of secondary amebic infection; involvement of the brain[4] and skin[9] occurs much more infrequently; and, while cases of amebic involvement of the spleen, genitourinary system, gallbladder, bone and pericardium have been reported,[1] they are sufficiently rare to relegate them to the field of medical curiosities rather than practical clinical entities.

Amebic hepatitis and amebic abscess of the liver are by far the most common and certainly the most important complications of amebiasis. Amebic infection of the liver occurs ten times more frequently in the male than in the female and is most common in the 30-50 year age group.[6] It is estimated to complicate about 5 per cent of intestinal amebiasis[6] and includes about 50 per cent of the surgical complications of amebic infection.[5] In a review by Ochsner and DeBakey[6] of 287 cases of liver abscess admitted over a 14 year period to Charity Hospital and Touro Infirmary in New Orleans, it was found that 181 (63 per cent) were amebic and 106 (37 per cent) were non-amebic.

The amebae may gain access to the liver by direct invasion, by lymphatic spread or by way of the portal circulation. There seems little doubt that invasion by way of the portal circulation is by far the most common, if not the only, route of entry. Once the organism has reached the liver, local vessel thrombosis occurs followed by infarction with dissolution of tissue by the cytolytic ferment of the ameba, carrying the process to abscess formation. Amebic abscesses are more frequently solitary (65 per cent and are more commonly found in the right lobe (85 per cent), usually near the dome of the liver.[7]

Only about half of the cases of amebic abscess of the liver give an antecedent history of diarrhea. The dysenteric symptoms have usually occurred within two or three months previous to the liver involvement, although cases have been reported in which amebic dysentery antedated the liver complication by 20 to 30 years. The onset may be sudden or gradual with fever, chills, sweats, weakness, loss of weight and pain in the right upper quadrant or right lower chest region. The pain may be deep and constant or it may assume the character of pleuritic pain with aggravation upon inspiration and referral to the right shoulder region as a result of involvement of the diaphragmatic pleura. Tenderness and increased resistance are usually present in the right upper quadrant. Some degree of hepatomegaly is almost invariably present. There may be diminution of breath sounds and reasonance along with a few fine rales over the right posterior lung base as a result of compression atelectasis from elevation and reduced mobility of the right hemi-diaphragm.

Laboratory procedures may be very valuable in confirmation of the diagnosis. A moderate leukocytosis is usually present; however, in the presence of secondary infection the leukocyte count may be quite high. Demonstration of amebae in the stool depends to a large degree on the care and frequency with which stool examination is

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†From the Department of Medicine of Louisiana State University School of Medicine, New Orleans.

done. In several large series of cases of amebic hepatic abscess, stools have been found positive for ameba histolytica in 11 to 36 per cent of cases.[6] Proctoscopic examination may be helpful in visualization of ulceration in the lower bowel and in obtaining material for microscopic examination. The complement fixation test is of apparent value, but the difficulty at present in preparation of the antigen precludes its general use.[3] X-ray examination is unquestionably the most valuable laboratory procedure in that 85 to 90 per cent of cases may be expected to show positive roentgenographic signs.[6] These consist in the main of elevation and immobility with or without local bulging or "steepling" of the right hemi-diaphragm. The use of thorium dioxide and lipiodol have been advocated by some observers as an adjunct in roentgen diagnosis of hepatic abscess.[10] However, in light of our incomplete knowledge of the effect of these substances on the liver, their use is not generally recommended.

The complications of amebic abscess of the liver are concerned with secondary infection and rupture into adjacent tissues. The more common sites of rupture are into the lung, pleural space and peritoneal cavity. Occasionally rupture may occur into the pericardial cavity or some adjacent organ such as the spleen, kidney or colon.

The treatment of amebic abscess is, in the main, conservative consisting of the administration of emetine hydrochloride (gr. 1 daily subcutaneously for 7 to 10 days) with or without aspiration of the abscess. In general, it may be said that most cases will require one or two aspirations. Some cases, however, subside with the use of emetine alone. At times, the decision to aspirate is not easily made; one must be guided by the degree of the response to emetine and the presence or progression of the x-ray signs of bulging or "steepling"" of the diaphragm. The pus obtained by aspiration is usually of the typical reddish-brown "anchovy sauce" type, contains demonstrable amebae rather infrequently, and is sterile unless secondary infection has occurred. There seems to be no virtue in the instillation of emetine hydrochloride into the abscess cavity; perhaps, the instillation of penicilln into the abscess cavity after aspiration may retard or prevent the occurrence of secondary infection. Open drainage is indicated only after secondary infection has occurred.

In addition to the general factors of virulence of the organisms and host resistance, prognosis depends on the multiplicity of the lesions, presence or absence of secondary infection and other complications, and the type of therapy employed. Review of analysis of a large series by Ochsner and DeBakey reveals the following approximate overall mortality figures: 10 per cent in cases with solitary abscesses; 60 to 100 per cent in those with multiple abscesses; about 40 per cent in complicated cases and about 75 per cent in those cases with secondary infection. In general, the mortality with open drainage is about seven to eight times that with the more conservative aspiration procedure. In a collected series of about 5,000 cases, the mortality from open drainage was 45 per cent, while only 6.7 per cent in those treated with emetine and aspiration.[7] The decline in overall mortality of amebic liver abscess is strikingly proportional to the gradual acceptance of aspiration and emetine as the therapy of choice.

PLEUROPULMONARY AMEBIASIS

Although cases of supposed primary amebic pneumonitis have been recorded, it seems doubtful that primary infection of the lung occurs in the abscence of previous bowel infection. Probably 75 per cent or more of amebic pleuropulmonary involvement occurs as a complication of rupture of an hepatic abscess through the diaphragm, and it is likely that the remainder result from hematogenous spread from the intestinal tract. About 15 per cent of amebic liver abscesses are complicated by pleuropulmonary lesions which may take the form of a bronchohepatic fistula, a lung abscess, or an empyema, or any combination thereof.

The clinical manifestations of pleuropulmonary involvement vary according to the mode and extent of the infection. In amebic

lung abscess of hematogenous origin the clinical picture is little different from that seen in pyogenic lung abscess. In cases which complicate liver abscess, pleuritic pain in the right lower chest accompanied by dyspnea and an unproductive cough, together with an increase in the gravity of the patient's general symptoms, usually herald the extension of the process into the chest. Expectoration of anchovy sauce sputum containing *Endameba histolytica* is practically pathognomonic of bronchohepatic fistula. The physical findings over the right lower chest may be those of fluid, consolidation or cavitation depending on the dominant process present. However, the usual findings are inspiratory lag, dullness, suppression of breath sounds and fine rales. The x-ray findings are usually those of pleural reaction, fluid and consolidation in the lower half of the lung field. However, in some cases, the roentgenographic findings are quite characteristic, showing a triangular density extending from a high right hemi-diaphragm toward the hilus of the lung.

Treatment is generally conservative. In cases with bronchohepatic fistulae the administration of emetine hydrochloride and postural drainage is usually all that is necessary. Aspiration should be done if pleural effusion is present. Open drainage is reserved for those cases in which definite secondary infection of the pleural space has occurred.

Prognosis depends largely on the type of involvement and the therapy employed. Bronchohepatic fistula and lung abscess communicating with a bronchus allowing for good drainage carry the best prognosis, mortality being 5 to 10 per cent, whereas in those cases with empyema mortality greatly increases to about 75 per cent.

BRAIN ABSCESS

Amebic brain abscess occurs relatively rarely and almost never in the absence of amebic infection of the liver and/or lungs. The clinical picture is much the same as that presented in pyogenic abscess except that the course toward an invariably fatal termination in spite of therapy is inexorably more rapid.

AMEBIASIS CUTIS

Ulceration and abscess of the skin is a rare complication of amebiasis and usually occurs as a secondary manifestation of rupture or drainage of an hepatic or pericolic abscess through the skin. Occasional cases have been reported as a result of perianal extension of amebic rectitis. Clinically, there is swelling and induration followed by necrosis resulting in an ulcerated area having an irregular contour with gangrenous overhanging edges. The condition is similar in appearance to the post-operative synergistic gangrene described by Meleney due to microaerophilic nonhemolytic streptococci. Amebae may be demonstrated in necrotic tissue removed from the edges of the ulceration. Treatment consists in the administration of emetine hydrochloride and wide excision of the ulcerated area with the high-frequency knife. Wyatt and Buchholz[9] reported a mortality of 42.3 per cent in a review of 26 cases.

SUMMARY

Extra-intestinal amebiasis is discussed relative to its incidence and importance. Diagnosis and management of hepatic and pleuropulmonary involvement are dealt with in some detail. Conservative therapy with emetine hydrochloride and aspiration is emphasized.

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AN EVALUATION OF ANTI-AMEBIC DRUGS

KENNETH G. NIX, M. D.

NEW ORLEANS

INTRODUCTION

By definition the clinical term "amebiasis" includes all conditions caused by the invasion of the tissues of man by the pathogenic ameba known as *Endamoeba histolytica*. The invasion of the various tissues of the body occurs primarily through the mucous membrane of the large intestine and less often through that of the lower portion of the ileum. The term "amebic dysentery," formerly used to indicate all infections with *Endamoeba histolytica*, with the exception of amebic abscesses of various organs, is now properly restricted to infections in which the prominent symptom is a bloody diarrhea induced by this parasite.[1]

The problem of treating amebic infection is arousing great interest among medical groups throughout the countries of the world. While military medical men have been conducting first-hand, battle-front research in the treatment and control of amebiasis throughout the world, civilian research has been continuing through the war years in America. From the islands of the Pacific, from the Orient, from the Mediterranean area and from countries all over the world have come reports on various drugs used in the treatment of this scourge of amebic infection which has plagued armies and peoples throughout history. Many strides have been made as a result of wartime research in amebiasis.

The end of the war, however, has not lessened the problems of amebiasis control. On the contrary, it has brought them closer home. As millions of our military men and women have already returned to America from regions where amebiasis is endemic or even epidemic, there is an obvious likelihood of a greatly increased incidence of amebic infections in this country. An evaluation of the research in amebiasis and the drugs used in the treatment of this condition is necessarily in order at this time. In this paper the writer will attempt to provide a concise summary of the medical developments which have taken place in the treatment and control of amebiasis during the past five years or so.

HISTORY

The causative organism of amebiasis and amebic dysentery was first discovered in 1875 by Lösch while examining a stool of a patient with dysentery in St. Petersburg, Russia. At that time he gave to the pathogenic organisms the name of "Amoeba coli," but this has since been changed to *Endamoeba histolytica*. It is still questionable whether other observers had seen this ameba prior to Lösch. However, it is generally believed that the credit for the discovery of the pathogenic species belongs to him.

Koch, in 1883, observed five cases of dysentery in Egypt, two of which were complicated with abscess of the liver, and in the ulcers occurring in the large intestine he found numerous amebae and in sections these were also found deep in the tissues at the base of the ulcerations, as well as in the capillaries of the liver, close to the abscess walls.

In 1886, Kartulis published a paper describing his results in the study of 150 cases of dysentery in Egypt in all of which he demonstrated amebae identical with those described by Lösch. Also Kartulis was successful in producing dysentery in cats by rectal injection of feces containing amebae.

Sir William Osler, in 1890, was the first one in the United States to demonstrate the amebae in a case of dysentery and liver abscess, and his observations were followed in the same year by those of Stengel. In 1891, J. H. Musser, Sr.,[2] at the University of Pennsylvania also demonstrated amebae in a case of dysentery complicated by abscess of the liver. This was followed in the same year by the work of Dock.

One of the classics on the subject of amebiasis was published in 1891 in the form of a monograph by Councilman and LaFleur who reported on 14 cases studied at the Johns Hopkins Hospital. They concluded that amebic dysentery is a clinical entity

and that it is characterized by definite pathologic lesions produced by the amebae.

In 1893 and 1894, Quincke and Roos published the first description of the cysts of *Endamoeba histolytica*. A more accurate description of the cysts of this parasite was published by Huber in 1903. Schaudinn in 1903 accepted the name for the genus previously proposed by Casagrandi in 1895, but named his pathogenic species, *Endamoeba histolytica*, and the name *Endamoeba coli* to the non-pathogenic species.

The first observer to produce an abscess of the liver in an experimental animal after the production of dysentery by the rectal injection of *Endamoeba histolytica* was Harris (1901). Later amebic abscess of the liver was produced in this manner by Craig (1905), Huber (1909), Wenyon (1912), Baetjer and Sellards (1914), and Dale and Dobell (1917).[1]

GEOGRAPHIC DISTRIBUTION

Amebiasis is worldwide in distribution. It can no longer be considered a tropical disease. Craig[1] states that the infection is widespread throughout the United States and conservatively estimates that from 5 to 10 per cent of the population of this country is infected with *Endamoeba histolytica* and that at least 50 per cent of individuals infected with this parasite have definite symptoms which are caused by its presence. Faust[3] believes that the incidence in this country may well be even higher than 5 to 10 per cent because the samplings of the population are perhaps too scattered and isolated to be completely representative of the degree of infection.

While amebiasis has a world-wide distribution the severe lesions and symptoms which are present in amebic dysentery occur much more frequently in the tropics and the warmer portions of the sub-tropics than in temperate and cold climates. In the United States cases of amebic dysentery have been reported from practically every state in the Union and there can be no doubt that many cases are wrongly diagosed annually, because of the widespread belief that this type of dysentery occurs only in the tropics or sub-tropics. According to Craig,[1] amebic dysentery is most frequently observed in the United States in Louisiana, Texas, Georgia, Florida, California, Mississippi and Alabama, but a considerable number of cases have been reported from Virginia, Maryland, the District of Columbia, and the Carolinas.

CLASSIFICATION OF AMEBIASIS

Just as in the consideration of the symptomatology of amebiasis it is essential to understand the method by which *Endamoeba histolytica* produces lesions in the intestine and the character of these lesions, it is equally as essential in the choice of specific therapy to have a working, clinical classification of the disease. Specific treatment and the use of certain specific drugs will naturally vary with the location of the lesions and the severity of the infection.

Many clinical classifications of the various types of amebiasis have been proposed by different authorities but the following seem to be the most useful. Dobell and Low[4] in 1922 outlined the following simple classification: (1) carrier; (2) general amebiasis; (3) amebic diarrhea; and (4) amebic dysentery.

The clinical classification by D'Antoni,[5] a modification of Craig's classification, appears to be the most useful to the writer. It is based upon symptomatology and it should be remembered that the various clinical classes mentioned tend to merge into one another and that an individual who may be placed in one class may, at any time, develop symptoms characteristic of one or more of the other classes.

CLINICAL CLASSIFICATION OF AMEBIASIS

1. *Asymptomatic amebiasis*

The patient is not cognizant of symptoms and the lesions are not confined to specific areas.

2. *Symptomatic amebiasis*

a. *Asyndromic* (formes frustes): There is a mild toxemia and vague gastrointestinal irritation with lesions usually not confined to specific areas.

b. *Syndromic*: There may be symptoms simulating chronic appendicitis, peptic ulcer, chronic cholecystitis with lesions usually confined to the cecal area.

c. *Dysentery* (acute or chronic): There

are symptoms of dysentery with the lesions throughout the colon, especially the rectal and sigmoid areas.

d. *Hepatitis and liver abscess*: The symptoms usually are fever, pain and tenderness in the liver area with liver lesions.

e. *Involvement of other organs (extra-intestinal)*: Abscess of lung, brain, kidney, amebiasis cutis, and so on.

LOCATION OF LESIONS

The location of the lesion in the intestine is important from both a prognostic and therapeutic point of view. It has been found that the most advanced and oldest lesions will usually be found in the ileo-cecal region, including the ileo-cecal sphincter, the distalmost segment of the ileum, the cecum, the appendix and the ascending colon; next the rectum and sigmoid colon, then the sigmoid and hepatic flexures—regions where stasis of the fecal mass occurs most commonly.

Clark[6] (1925) found the order of frequency of ulceration was the cecum, ascending colon, rectum, sigmoid, and appendix. Craig[7] (1934) in 78 cases found lesions in the ileo-cecal region, the descending colon, and the rectum in 57 cases; lesions along the whole length of the colon in 12 cases, but most severe below the ileo-cecal valve and in the rectum; while in nine cases the rectum and the sigmoid alone showed active lesions, with healed lesions in the ileo-cecal region.

Faust (1940) and D'Antoni[8] (1941) found that the preponderance of lesions occurs in the cecal area and next in the rectal area and that these two levels of involvement primarily condition the types of symptoms in intestinal amebiasis, namely cecal amebiasis and sigmoido-rectal amebiasis.

CLASSIFICATION OF AMEBACIDAL DRUGS

A. *The Emetine Group*
   1. Ipecacuanha (ipecac)
   2. Emetine hydrochloride
   3. Emetine bismuth iodide

B. *The Oxyquinoline Derivatives*
   1. Chiniofon
   2. Vioform
   3. Iodoquin
   4. Diodoquin

C. *The Organic Pentavalent Arsenicals*
   1. Carbarsone
   2. Treparsol
   3. Acetarsone

D. *Miscellaneous Drugs*
   1. Succinylsulfathiazole
   2. Penicillin
   3. Trilactic
   4. Kurchi bark
   5. Bismuth subnitrate
   6. Shadocol (sodium tetraiodophenolphthalien)

THE INDIVIDUAL AMEBACIDAL DRUGS

Ipecacuanha: This particular drug is the dried root of Psychotria ipecacuanha which is native in Brazil but is cultivated in India, the Straits Settlements, and the Federated Malay States. The efficiency of the drug is dependent on its two chief alkaloids, emetine and cephaline. Of the two alkaloids emetine is by far the more potent as an amebacide, although cephaline does possess some amebacidal action. This drug was used for years in the treatment of amebiasis by the natives of Brazil, on the European continent, and in this country. While the drug possesses all the amebacidal properties of emetine, its use in the modern treatment of amebiasis is definitely limited due to the difficulty of administration and the excessive discomfort caused by it.

Emetine: Emetine was first described in 1817 by Pelletier, the discoverer of quinine in cinchona bark. Bardsley in 1829 was apparently the first person to use emetine in diarrheas and dysenteries. In 1912 Vedder demonstrated that emetine is a powerful amebacide to free-living amebae in cultures, and the same year Rogers reported good results from the drug in the treatment of amebic dysentery and hepatitis.

Emetine is an alkaloid of ipecacuanha and is used in the form of the hydrochloride salt because of its greater solubility. It is prepared in ampules containing one grain of emetine hydrochloride in 1 c.c. of solution. The dosage for adults consists of one grain subcutaneously, not to exceed 12 grains within a period of 40 days. The drug should never be given to children under eight years of age and to those over this age

the dose must never exceed one-third of a grain daily. The patient should be hospitalized and 1 grain of the drug is given subcutaneously per day for adults on successive days for a period not to exceed eight to 10 days and the course should not be repeated within a shorter interval than one month.

Emetine relieves the acute symptoms in approximately 85 per cent of the cases. However, despite the apparent highly amebacidal property of emetine *in vitro*, it is generally agreed that the alkaloid alone does not result in the cure of amebic infections in more than 10 to 15 per cent of patients. It is relatively efficient in the treatment of liver abscess and amebic hepatitis and at present the only drug available. It should be reserved only for use in the control of the acute symptoms of severe diarrhea and dysentery. Emetine has a direct lethal action on the ambae as demonstrated *in vitro* and is more effective against motile forms than against the cysts. Concentrations of emetine necessary to kill the cystic forms cannot be safely obtained in man.

In therapeutic doses emetine will produce nausea and vomiting when taken by mouth. Emetine frequently causes toxic symptoms, especially noted when its action is cumulative from too high dosage or from prolonged therapeutic use. It is a "general protoplasmic poison," and causes hyperemia, cloudy swelling and cellular degeneration in the liver, heart, kidneys, and skeletal muscles. Emetine as a result of its myotoxic action may produce cardiac arrhythmias and can cause a severe acute degenerative myocarditis which may result in sudden cardiac failure or death. Myositis, muscular weakness, tremors and pain, especially in the arms and legs, and gastrointestinal symptoms are also prominent manifestations of emetine poisoning.

Dack and Moloshok[9] (1947) have recently reviewed a series of 21 cases of amebiasis which were treated with emetine hydrochloride. Nine out of these 21 cases developed toxic cardiac effects with changes in their electrocardiograms. They found that the commonest electrocardiographic abnormality was inversion of the T waves, usually involving all the standard leads. All nine patients in their series showed inversion of the T waves in leads II and III while six showed inversion of the T wave in lead I and 4 in lead IV-F. There was no deviation or depression of the ST segment, but there were abnormalities of the QRS complex in two cases. The duration of the abnormal findings found varied from six weeks to two months or longer. They found, however, that the neuromuscular and gastrointestinal symptoms of emetine poisoning preceded the electrocardiographic changes in the majority of cases. This would lead one to doubt if abnormal changes in the electrocardiogram are in keeping with an early diagnosis of emetine poisoning. They should be taken in every case receiving emetine, however. Earlier Boyd and Scherf[10] (1941) reported similar changes in the electrocardiogram in acute emetine intoxication.

The use of emetine is contraindicated in cases with myocardial, kidney and liver damage. It is also definitely contraindicated in children under eight years of age and is best not used during pregnancy.

Emetine - Bismuth - Iodide: DuMez, in 1915, in the Philippine Islands first called the attention of medical practitioners to this compound. It was reported upon favorably by Low and Dale (1916) and by Dobell (1916) as efficient in the treatment of carriers and of patients resistant to emetine alone. This combination is highly regarded by many English authorities who consider it the drug of choice in the treatment of amebic infections.

Emetine-bismuth-iodide contains 29 per cent iodine, 12 per cent bismuth, and 58 per cent emetine. The toxicity of this preparation is essentially that of emetine. The dose of emetine-bismuth-iodide that should be employed is 0.2 gram (3 grains) administered once a day for 21 consecutive days. Rest in bed to prevent or lessen nausea and liability to cardiac failure is recommended. This combination is never used in the United States in the treatment of amebiasis.

Chiniofon (anayodin and yatren): This is an iodine compound having the chemical

formula of 7-iodo-8-hydroxyquinolin-5-sulphonic acid and contains 26 to 28 per cent iodine. It was introduced as an amebacide in 1921 by Muhlens and Menk. In therapeutic doses it is non-toxic by mouth or by rectum. Two deaths have been reported from its intravenous use in which liver damage was the outstanding feature.

Chiniofon is prepared in keratin-coated or uncoated pills each containing 4 grains (0.25 gram). Three to four pills (12-14 grains) are given to an adult by mouth three times a day for a period of eight to 10 days. For children one grain per 10 pounds of body weight is given three times a day for approximately the same period of time. Following meals 12 to 16 grains (three or four tablets) are given by mouth for a period of seven days. If no *Endamoeba histolytica* are found in the stools over a period up to six months, no further treatment is necessary. If the stools remain positive, the treatment is repeated following a rest period of at least seven days. The drug may be administered without interfering with the patient's daily routine, and no precautions are necessary regarding diet or exercise except in cases manifesting symptoms.

Chiniofon is an efficient amebacide and has a proved efficacy of approximately 90 per cent or better. It should not be used in the presence of iodine intolerance or liver damage and must be given with caution to patients with thyroid disease.

Vioform: Chemically, this compound is iodochlorhydroxyquinoline, containing between 37.5 and 41.5 per cent iodine. It is prepared in the form of gelatin capsules each containing 4 grains (0.25 gram). The dose for adults is 4 grains (one capsule) three times a day for 10 days. Twice this dose is recommended for severe infections. For children the dose is one-third grain per 15 pounds of body weight three times a day for 10 days. The course may be repeated following a rest period of seven days. There is no interference with the patient's daily routine.

In the treatment of amebiasis, vioform has an efficacy of approximately 80 per cent. It has also been used since its introduction as a substitute for iodoform as a dusting powder for application to wounds, burns, skin eruptions, and so on.

The toxicity of vioform is slight unless therapeutic doses are exceeded. It is considered more toxic than chiniofon but less toxic than carbarsone. Contraindications for its use are essentially the same as for chiniofon.

Diodoquin: Chemically, it is an iodine compound in which the sodium sulfonate radical of chiniofon is replaced with a second iodine atom, increasing thereby the iodine content to 63.9 per cent. The drug is prepared in tablets containing 3.2 grains (0.21 gram).

For adults the dose recommended in the treatment of amebiasis is from 22.5 to 30 grains (seven to 10 tablets) daily for a period of two to three weeks. The dose for children consists of one tablet daily per 15 pounds of body weight. The tablets are given in divided doses following meals, and the course may be repeated after a rest period of seven to 10 days.

Diodoquin has been found to be non-toxic in therapeutic doses and only an occasional headache and mild gastrointestinal disturbance if any have been reported from its use. It is considered by most authorities the least toxic of the amebacidal drugs.

Summarizing the clinical results observed in his investigation of the use of diodoquin in the treatment of amebiasis, D'Antoni[11, 12] (1942-43) stated: "On the basis of 126 cases, diodoquin would seem to be more than 92 per cent effective in single cases and 99 per cent effective in all patients treated. No drug previously used in the treatment of amebiasis has given such consistently satisfactory results." The drug has also been reported on very favorably by Hummel[13] (1937-1940) and Almy[14] in this country and by Morton[15] and Manson-Bahr[16] in England.

Manson-Bahr[16] states that diodoquin "is well tolerated. The great advantage of this simple treatment is that in the vast majority, it destroys the cysts of *E. histolytica* and is, therefore, especially valuable in steriliz-

ing 'cyst-carriers.' It can readily be taken by ambulant patients and, therefore, eliminates the necessity of hospitalization."

Craig[1] believes that diodoquin will be of definite value in the prophylactic treatment of amebiasis and that further observations may well demonstrate that it is the most specific drug that we possess for the treatment of this infection.

Carbarsone: This drug was first prepared by Ehrlich and is a white crystalline solid without taste or odor, almost insoluble in water but soluble in alkaline aqueous solutions, and contains 28.85 per cent of arsenic. The chemical formula of this compound is 4-carbaminophenylarsonic acid.

Carbarsone is directly amebacidal by virtue of its arsenic content. Anderson and Reed[17] (1931) first introduced this compound as a specific in the treatment of amebiasis. It is more effective than acetarsone and has a therapeutic index eight times higher. Like chiniofon, the action of carbarsone on motile forms, although effective, is not as rapid as that of emetine. Carbarsone does not act on amebae in abscesses of the liver and other organs. The drug is active against cysts.

The adult dose of carbarsone is 0.25 gram (4 grains) taken orally twice a day for 10 days and the course of treatment may be repeated in resistant cases after an interval of 10 days. Carbarsone can also be given rectally as a retention enema and is used in this manner for acute dysentery with motile amebae in the stool or dysentery cases that have proven refractory to the oral administration of the drug. Anderson and Reed[18] (1934) recommend its employment daily for five days at least in the form of retention enemata consisting of 200 c.c. of a 2 per cent sodium bicarbonate solution containing 1 per cent carbarsone. They also recommend that a rapidly acting sedative as sodium amytal be given orally in a dosage of 0.2 grams (3 grains) in order to produce sleep, thus allowing the patient to retain the drug and if the enema is expelled it should be repeated until at least five enemata have been retained.

Carbarsone is absorbed readily after oral administration and is excreted rather slowly in the urine. Rest periods between courses are therefore imperative to prevent cumulative toxic effects. Carbarsone appears to be one of the most innocuous of the organic arsenicals. Considering the wide use of the drug, few cases of serious poisoning have been reported. Despite the para position of the amino group, serious optic damage is almost unknown but caution should be used in its administration. Skin rashes of varying severity but usually mild, and localized edemas are occasionally observed. Exacerbation of diarrhea, mild nausea and vomiting, and vague abdominal pains may sometimes occur. Its use is contraindicated in the presence of liver and kidney disease.

Reed[18] (1935) is of the opinion that carbarsone is the best of all amebacidal drugs. He administered the drug to 330 patients with amebiasis, only three of whom showed symptoms of intolerance, and the drug was successful in eliminating the infection of 90 per cent of these patients. Craig[1] (1944) believes that carbarsone, in the treatment of carriers and mild infections with *Endamoeba histolytica* may be relied upon to eliminate the infection in from 85 to 95 per cent of the cases, while a repetition of the drug and course of treatment will result in the elimination of most of the resistant infections. However, he believes also that since the drug is an arsenical and more toxic than the iodine preparations, it is generally less useful than the latter and that carbarsone treatment should be reserved for those infections which have proven incurable with the iodine compounds.

Treparsol: This drug is an arsenobenzolic derivative of the salvarsan type and is furnished in tablets containing 0.25 gram (4 grains). It has been used in the treatment of amebic dysentery and amebiasis with good results but it has the disadvantage of the toxicity inherent in all arsenic compounds, although the evidence points to its being less toxic than acetarsone.

The dose of the drug as recommended by Brown[19] of the Mayo Clinic is 0.25 gram (4 grains) three times a day with meals for four days; cessation of the treatment for

ten days; and finally 0.25 gram three times a day for four days. The tablets should be chewed with the food as this causes greater dispersion of the arsenic.

Acetarsone: This compound, which is also known as Stovarsol, was introduced by the French for the treatment of syphilis, and is a synthetic arsenical (acetylaminohydroxyphenylarsonic acid) containing from 27.1 to 27.4 per cent of arsenic. It was formerly extensively used in the treatment of amebiasis and was administered in tablet form by mouth, each tablet containing 0.25 gram (4 grains) of the compound. It is little used today.

OTHER DRUGS EMPLOYED IN TREATMENT

The bacterial flora of the intestines has some bearing on the virulence of amebic infection. A purely amebic infection is rare, for every infection is complicated by the presence of pathogenic bacteria which have penetrated into the tissues via lesions produced by the amebae.

Sokoloff[20] (1945) has demonstrated that the virulence of *Endamoeba histolytica* may be increased when it is inoculated along with certain bacteria into experimental animals. He found that streptococci and staphylococci apparently enhance the multiplication of *Endamoeba histolytica;* that *Clostridium perfringens* (of the *B. welchii* group) and *Lactobacillus acidophilus* induce the encystment and coagulation of the free-living amebae.

Many of such cases complicated by secondary bacterial invasion do not respond favorably to specific anti-amebic therapy and tend to become chronic. It has been found that by combating the bacterial infection present in the colon and following this with amebacidal therapy that many of the so-called "resistant" or chronic forms of the infection can be treated successfully. Three or four of such therapeutic agents will be briefly discussed below.

Succinylsulfathiazole: Little information has as yet been published on the use of sulfonamides or of penicillin to combat secondary bacterial infection in amebiasis. However, marked benefit has been reported by Hargreaves[21] (1945) in severe amebic infection following the administration of sulfasuxidine (succinylsulfathiazole) by mouth in conjunction with penicillin intramuscularly and he has seen marked improvement after the use of penicillin alone. The total dosage recommended by Hargreaves was 80 grams given in divided doses of 1 gram every three to four hours. A standard course of anti-amebic treatment was given after completion of the antibacterial therapy.

Penicillin: As already mentioned in the preceding discussion, penicillin has proved to be a very useful adjunct in the treatment of chronic cases of amebic colitis by virtue of its ability to combat secondary bacterial infection. In addition to Hargreaves another English writer, Willmore[22] (1945), reports similar experiences with penicillin.

Hargreaves and Willmore recommended an initial injection of 100,000 units of penicillin intramuscularly to be followed by 33,000 units at three-hourly intervals with a total dosage of two million units.

Trilactic is the anhydrous form of lactic acid which dissolves slowly in water, decreases the pH of the large intestine, and promotes the growth of acidophilic bacteria. There is some indication that as a general rule bacteria which lower the pH inhibit the multiplication of amebae. *In vitro* experiments carried out at the University of California by Sokoloff[20] and Kessel (1945) have demonstrated a definite antibiotic action of lactic acid. They found that lactic acid causes coagulation of almost all amebae in cultures within 30 minutes in concentrations of 0.0098; changes in the nucleus of amebae and arrested motility; and that the mode of action may be on the amylase which is present in large quantities in the body of all amebae.

Trilactic was given by Sokoloff to 62 patients affected with acute and chronic amebic infections in the form of the anhydrous form of lactic acid. For the acute dysentery 40 to 50 grams of trilactic were given daily in divided doses of four and given in pulverized rice or semi-fluid oatmeal for seven days and then gradually decreased after the acute stage was arrested. For chronic

amebiasis without dysentery three to four tablespoonfus daily divided into two doses. morning and at night were given. In 34 cases, or in 54 per cent, complete recovery was noted. In 19 per cent results were negative. In the remaining cases considerable improvement was observed. This is an entirely new form of anti-amebic therapy and demands more extensive clinical trial before a clear evaluation can be made of its amebacidal properties.

Kurchi Bark: The bark of a deciduous tree (Holarrhena antidysenterica) which is a native of the tropical Himalayas, has for many years had a reputation among the natives of India and adjacent regions as a remedy in diarrhea and dysenteries. The chemical composition of the bark has been thoroughly studied and several alkaloids have been isolated. At the present time the presence of four alkaloids in the bark of this tree has been demonstrated, that is, conessine, holarrhenine, kurchicine and kurchine, the latter occurring in the largest amount. The favorable results obtained in the treatment of amebiasis with this substance is due to a direct action on the amebae.

At the present time Kurchi-bismuth-iodide has largely replaced the administration of the total alkaloids by intramuscular injection, but the total alkaloids may be administered orally in the form of the standard fluid extract of kurchi bark, which contains about 0.032 gram (½ grain) of the alkaloids in 4 c.c. The dose of the extract is 8 c.c. three times a day for as long as four to six weeks in chronic infections. The dose of kurchi-bismuth-iodide varies from 0.25 gram (4 grains) orally twice a day for 10 days in chronic amebic infections to as much as 0.65 gram (10 grains) twice a day for 10 days in severe amebic infections.

Bismuth Subnitrate: For many years bismuth subnitrate has been used in the treatment of amebic dysentery. The drug alone was used for a while but has since been combined with emetine and this combined method is still in use by some today in the treatment of amebiasis. The subnitrate of bismuth acts by its antiseptic properties upon the bacteria of the intestine, reducing putrefaction, thus indirectly producing degenerative changes in the ameba because of this change in the environment of the organisms. In order for the drug to be effective it must be given in very large doses. A heaping teaspoonful, equivalent to about 180 grains in weight, mechanically suspended in almost a tumbler full of plain, or better, effervescent water, or in milk, is given every three hours day and night, lessening the amount only when improvement occurs.

Shadocol: Chemically, this drug is sodium tetraiodophenolphthalein (also called opacol and T.I.P.). The acidic form is prepared for oral administration as a suspension of the white acid body which is turned into the blue soluble sodium salt in the intestinal canal. The dye is absorbed from the intestinal canal, secreted by the liver, and excreted with the bile. One-half bottle of the dye is given to children under 6 years of age and all over this age are given one full bottle of the dye. A saline cathartic is given the next morning. No special dietetic measures and no other medication is employed with the dye.

Alexander, Park-Ross, and Stein[23] (1944) from South Africa reported 74 per cent sterilization of the intestinal canal following the administration of the shadocol in the treatment of amebiasis, based on immediate stool examinations. The follow-up on this drug is not too encouraging but results in their hands have been uniformly good.

TREATMENT OF AMEBIASIS

The treatment of amebiasis embraces the treatment of carriers and mild infections; amebic enteritis and amebic dysentery; amebic abscess of the liver, and other complications of this infection. However, it must be stated that at the present time we do not possess a *single* drug that will eliminate the amebic infection in *every* case. It is hoped that with further research and investigation in this field that a specific amebacide will be developed which will

eliminate the infection with *Endamoeba histolytica* in every case.

THE TREATMENT OF SYMPTOMLESS CARRIERS AND MILD INFECTIONS

It is agreed by most authorities today that in the treatment of carriers and mild infections chiniofon is usually the drug of choice. It is supplied in pills or tablets, each containing 0.25 gram (4 grains), and the dose for an adult is three tablets or pills given three times a day for a period of eight to 10 days. The full dose sometimes causes diarrhea so that it is well to commence with a smaller dose and increase it as it is well tolerated. Chiniofon is not a toxic drug and may be used safely in mass therapy and the treatment does not interfere with the occupation of the patient. In treating children the dose of chiniofon should be governed according to age and general condition.

One course of eight to 10 days with chiniofon is usually successful in eliminating *Endamoeba histolytica* in carriers and mild symptomatic infections but if not, the course should be repeated after an interval of 10 days.

In view of the very favorable reports upon diodoquin, Hummel,[13] D'Antoni[11, 12] and Morton,[15] it is felt that this compound will be equally efficient in such infections and, as it does not produce diarrhea, may be preferable, especially in children. For adults the dose recommended for oral administration is two tablets, each containing 0.21 gram (3.2 grains) three times a day for a period of 20 days. The dose for children consists of one tablet daily per 15 pounds of body weight.

If treatment with either of these compounds does not result in a cure, a course of treatment with carbarsone should be followed, 0.65 gram (4 grains) of this compound being administered twice daily, after the morning and evening meals, for a period of 10 days.

THE TREATMENT OF AMEBIC DIARRHEA OR ENTERITIS

If the patient is seen during an attack of severe diarrhea, rest in bed is indicated, and the administration of chiniofon as already described but beginning with not more than two pills three times a day for an adult. The number of pills may be increased progressively with improvement in the symptoms. If the diarrhea is particularly severe, it is sometimes wise to administer emetine hydrochloride subcutaneously in doses not to exceed 0.065 gram (1 grain) a day for not more than six to seven days, after which chiniofon should be administered as recommended.

If the patient is seen between diarrheal attacks, the treatment in such cases conforms very much to that as already described for carriers. Then, too, if there is a history of recurrent bouts of severe diarrhea, it may be necessary to repeat the course of treatment with chiniofon after a rest period of about 10 days until the infection is eliminated.

Diodoquin is highly recommended also for the treatment of amebic diarrhea or enteritis in dosages as already outlined. If neither chiniofon nor diodoquin is successful in combating the infection, a course of carbarsone should be given as already recommended in the treatment of carriers and mild symptomatic infections.

Care should be taken with regard to the diet in cases of amebic diarrhea. It should be fluid or semifluid in character and limited to substances that are easily digested.

THE TREATMENT OF ACUTE DYSENTERY

Bed rest is absolutely essential for patients with symptoms of acute dysentery. The acute symptoms can be controlled with one grain (0.065 gram) of emetine hydrochloride given subcutaneously once a day until symptoms subside but not to exceed 12 grains, or even better never to administer it for more than 10 days. *It should be emphasized that emetine hydrochloride is to be employed only to control the acute dysenteric symptoms.*

After the dysenteric symptoms are controlled with emetine, a standard course of chiniofon or diodoquin is administered as in the treatment of carriers and those presenting symptoms of enteritis. If either of these drugs fails, a full course of carbarsone or vioform is recommended.

D'Antoni[24] recommends that neoprontosil

or some other intestinal antiseptic be administered in conjunction with the chiniofon or diodoquin to combat any secondary bacterial infection that may be present.

The English[21] recommend the use of emetine hydrochloride subcutaneously in one grain daily until the dysenteric symptoms are relieved, not to exceed 10 days, followed by emetine-bismuth-iodide orally in the dose of three grains per day for 12 consecutive days. In severe cases this may be combined with daily retention enemata of chiniofon.

To secure the best results with chiniofon alone in the treatment of acute amebic dysentery, the use of high enemata containing chiniofon should be combined with treatment by mouth. When this is done, it is recommended that chiniofon be given by mouth in doses not to exceed 0.5 gram (7.5 grains) three times a day and daily enemas, best given at night, consisting of 200 c.c. of a 2 per cent warm water solution of chiniofon and retained for several hours if possible.

Routine stool examinations should be made after the disappearance of symptoms and the treatment with chiniofon or diodoquin repeated if they are found positive for *Endamoeba histolytica*.

THE TREATMENT OF CHRONIC AMEBIC DYSENTERY

There is a great difference of opinion regarding the best method for the treatment of chronic amebic dysentery. In general, however, the treatment of this condition depends upon whether the patient is seen during an acute exacerbation of the dysenteric symptoms or between the dysenteric attacks.

In this country if the patient is seen during an acute exacerbation, most authorities recommend the treatment of the acute symptoms as already described for acute amebic dysentery, while if the patient is seen during a quiescent period he should be given a course of chiniofon, diodoquin, or carbarsone, if the stools contain the amebae, in the manner already described. It is absolutely necessary for patients to be confined to bed during an acute exacerbation. Good nursing care and a proper diet are also absolute essentials.

Hargreaves[21] in England (1945) outlined the standard treatment employed in the treatment of Service Personnel with chronic amebic dysentery. It consisted of a 12 day course of emetine-bismuth-iodide together with daily retention enemata of chiniofon (200 c.c. of a 2.5 to 5 per cent solution at body temperature). This was followed by a course of carbarsone, four grains twice daily for 12 days. If the patient had dysenteric symptoms, this course was preceded by six daily injections of emetine hydrochloride of one grain each subcutaneously. Secondary bacterial invaders were controlled in severe cases by the use of penicillin and sulfasuxidine.

In contrast to the above method of treating chronic amebiasis Adams[25] at the Liverpool School of Tropical Medicine has advocated a 21 day "blunderbuss" therapy which includes the following: (1) Emetine as aurementine by mouth in doses of one grain three times a day in capsules on odd numbered days; (2) stovarsol or carbarsone in doses of 4 grains three times a day on even numbered days with a retention enema of 8 to 15 oz. of freshly prepared 2½ per cent quinoxyl in the evening, changing to a 4 per cent solution halfway through the course; (3) bismuth subnitrate in doses of 60 grains three times a day in milk to be given every day; (4) the retention enema is preceded by a rectal wash-out with a weak solution of sodium bicarbonate solution to remove the mucous.

A series of 80 cases were studied using the two different methods outlined by Hargreaves and Adams, dividing the cases equally. Out of the 40 cases tried on the Standard Treatment advocated by Hargreaves only six (or 15 per cent) were not cured; of the 40 cases tried on the Liverpool 21 day "blunderbuss" treatment 21 cases (or 52 per cent) were not cured.

TREATMENT OF COMPLICATIONS OF AMEBIASIS

According to Craig,[1] the most important of the complications of amebiasis are amebic hepatitis, amebic abscess of the liver and amebic abscess of the lung.

The treatment of amebic abscess of the liver and of the lung is largely a surgical problem, but the early recognition of amebic hepatitis and beginning abscess formation

is essentially a medical problem. The only drug effective in the treatment of such extraintestinal lesions of amebiasis is emetine hydrochloride. For the treatment of extraintestinal amebiasis, emetine hydrochloride is given in doses of 1 grain daily subcutaneously for a period not to exceed 10 days. It should not be repeated in less than a month.

Sodeman and Lewis[26] (1945) in a review of the last 33 cases of amebic hepatitis seen at the New Orleans Charity Hospital and the U. S. Marine Hospital at New Orleans concluded that early diagnosis led to effective treatment with emetine alone in many cases. Even at times when known abscess occurs treatment with emetine alone may be successful according to Hodson (1921).

CRITERIA FOR CURE

The treatment of amebiasis, particularly the dysenteric phases, is governed chiefly by stool examinations for *Endamoeba histolytica*. After each course of therapy stool examinations should be made and if positive for *Endamoeba histolytica* the treatment should be repeated. Craig[1] believes that at least three negative microscopic examinations of the stools, one week apart, should be secured before the patient is considered cured and thereafter, for at least three months, the examination of the stool should be repeated once a month.

However, it is my firm belief that a set criteria for cure cannot be established rigidly. One reason for this statement is the very evident fact that it is impossible to determine whether a patient has a relapse or a reinfection if the *Endamoeba histolytica* are found in the stools two weeks to three months after treatment. Therefore, it would seem advisable not to regard a particular amebacidal drug as an ineffective amebacide too hastily on this particular basis just because the trophozoites of cysts of *Endamoeba histolytica* reappear in the feces after specific treatment. It is a definite fact that there is no one drug or method of treatment which will cure every case of amebiasis today. It is hoped that with continued research and investigation in the field an effective, non-toxic amebacide will be discovered which will eliminate the infection in very case.

CONCLUSIONS

1. Amebiasis has been found in the United States wherever surveys have been conducted and the disease can no longer be properly referred to as a "tropical disease" *per se*.

2. Emetine is very effective in the treatment and control of the acute and severe symptoms of intestinal amebiasis, but clinical results are sufficient to prove that emetine hydrochloride does not, even when given in repeated courses of 12 grains with doses of 1 grain daily, cure many cases of endamebic dysentery, if by cure is meant the destruction of cysts in the majority of cases.

3. Emetine is the only drug available at the present time for the treatment of extraintestinal amebiasis and such complications of intestinal amebiasis as ameboma.

4. At the present time the drug of choice for the treatment of intestinal amebiasis is chiniofon. In therapeutic doses it is nontoxic by mouth or by rectum and is efficient in 90 per cent or more of the cases of amebiasis.

5. Diodoquin appears to be equally as effective as chiniofon in the treatment of intestinal amebiasis and, as it does not produce diarrhea following its administration, may be preferable, especially in children. However, it will be necessary to observe more cases treated with diodoquin before a true evaluation of its efficiency can be firmly established.

6. At the present time we do not possess a single drug that will eliminate the amebic infection in every case. It is hoped that with further research in this field a specific amebacide will be developed which will eliminate the infection with *Endamoeba histolytica* in every case.

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PREMATURITY—AN ORIENTATION*

ETHEL C. DUNHAM, M. D.
WASHINGTON, D. C.

Premature births constitute at least 5 per cent of the total births in the United States. This means that at least 150,000 premature infants were born in 1944. The proportion is probably considerably higher than this if a birth weight of 2,500 gm. or less is used as the criterion of prematurity. In New York City 7.3 per cent of the nearly 100,000 infants born in 1939 were premature on this basis.

It is necessary for clinical and for statistical purposes, to have a definite and objective delimitation between a premature and a mature infant. There is general agreement that a birth weight of 2,500 gm. or less is the best criterion for prematurity based on clinical indications of the need for special care and, in addition, on the sharp contrast in mortality among infants above and below this birth weight. In this connection Eastman[1] found that in the Johns Hopkins Hospital the fatality rate (percentage of deaths among infants in specified weight groups, born alive at the hospital) was 0.4 per cent among mature infants (those weighing at birth 2,500 gm. or more), whereas among premature infants (those weighing 1,000 to 2,500 gm.) it was 10.7 per cent. Even among infants on the borderline of maturity (those weighing 2,000 to 2,500 gm.) the fatality rate was 4.2 per cent—ten times that for mature infants. These figures apply to the period 1941-45.

The question has been raised of setting a low birth-weight limit for differentiation between abortions and premature live births. This is, however, more difficult than that of setting the upper limit of birth weight, since gestation period and birth weight are usually not closely correlated. In addition, infants have survived and grown to normal childhood whose gestation period or birth weight placed them in the "non-viable" obstetric classification. There are reports of the survival of a fairly large number of infants who weighed at birth less than two pounds and of a few who weighed less than one pound. The American Academy of Pediatrics recommends that all *live-born* infants weighing 2,500 gm. or less at birth should be classified as premature.

This brief orientation is made chiefly to point up the high mortality from prema-

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ture birth and the chief causes thereof as well as the chances for reducing this mortality and the prognosis for future development of these infants.

NEONATAL MORTALITY FROM PREMATURE BIRTH

The mortality rates for the United States birth-registration area are compiled from data on death certificates that show prematurity as the primary cause of death. Deaths of premature infants recorded as due to birth injury or congenital defect are classified by the Bureau of the Census in these latter cause groups according to the rules of the International List of Causes of Death.

The trend of the neonatal mortality rates from all causes and from premature birth in the past 11 years for the United States and for Louisiana are shown in figure 1.* The downward trends are apparent, as is the fact that the rates for Louisiana are considerably higher than those for the United States. Tables 1a and 1b show the figures on which these trends are based.

TREND OF NEONATAL MORTALITY FROM ALL CAUSES AND FROM PREMATURE BIRTH

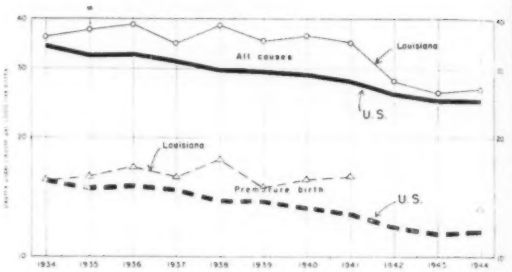

TABLE 1a

NEONATAL MORTALITY FROM ALL CAUSES AND FROM PREMATURE BIRTH; UNITED STATES, 1934-44

Year	Number of live births	Deaths in the first month from—All causes: Number	All causes: Rate per 1,000 live births	Premature birth: Number	Premature birth: Rate per 1,000 live births
1944	2,794,800	68,996	24.7	32,065	11.5
1943	2,934,860	72,632	24.7	33,513	11.4
1942	2,808,996	72,122	25.7	33,483	11.9
1941	2,513,427	69,559	27.7	32,278	12.8
1940	2,360,399	67,866	28.8	31,437	13.3
1939	2,265,588	66,383	29.3	31,260	13.8
1938	2,286,962	67,735	29.6	31,582	13.8
1937	2,203,337	68,887	31.3	32,524	14.8
1936	2,144,790	69,869	32.6	32,452	15.1
1935	2,155,105	69,834	32.4	32,021	14.9
1934	2,167,636	73,841	34.1	33,802	15.6

Based on data from U. S. Bureau of the Census for continental United States.

TABLE 1b

NEONATAL MORTALITY FROM ALL CAUSES AND FROM PREMATURE BIRTH; LOUISIANA, 1934-44*

Year	Number of live births	Deaths in the first month from—All causes: Number	All causes: Rate per 1,000 live births	Premature birth: Number	Premature birth: Rate per 1,000 live births
1944	61,050	1,654	27.1	857	14.0
1943	62,005	1,651	26.6	†	†
1942	58,093	1,639	28.2	†	†
1941	54,618	1,931	35.4	929	17.0
1940	50,916	1,869	36.7	853	16.8
1939	48,844	1,738	35.6	775	15.9
1938	48,867	1,883	38.5	891	18.2
1937	46,006	1,622	35.3	778	16.9
1936	43,828	1,703	38.9	773	17.6
1935	42,270	1,600	37.9	716	16.9
1934	43,003	1,567	36.4	716	16.7

*1934-40, by place of occurrence; 1941-44, by place of residence.
†Not available.
Based on data from U. S. Bureau of the Census.

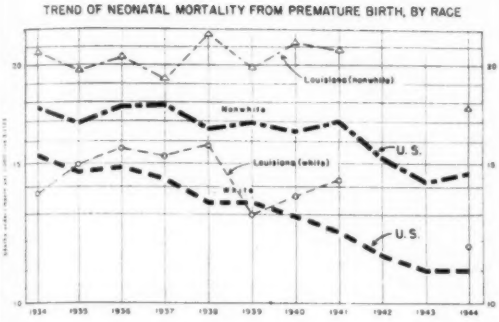

Figure 2 shows the neonatal rates by race for the same period. The downward trend in the United States is apparent for both white and non-white premature infants. In Louisiana the trend in the mortality rate for white infants was irregular, and the rate in 1944 was somewhat higher than that for the United States. The Louisiana rate for non-white infants was maintained at a much higher level than the rate for the United States in the entire period 1934 to 1944. In 1944 there was a considerable decrease, however, in the Louisiana rate for non-white infants, but it was still much higher than that for the United States. The figures on which these trends are based are shown in tables 2a and 2b.

*Charts and tables based on Census Bureau data prepared by Children's Bureau, Social Security Administration, Federal Security Agency.

TABLE 2a

NEONATAL DEATHS FROM PREMATURE BIRTH, WHITE AND NON-WHITE; UNITED STATES, 1934-44

Year	Number of live births		Deaths in the first month from premature birth			
			Number		Rate per 1,000 live births	
	White	Non-white	White	Non-white	White	Non-white
1944	2,454,700	340,100	27,109	4,956	11.0	14.6
1943	2,594,763	340,097	28,670	4,843	11.0	14.2
1942	2,486,934	322,062	28,588	4,895	11.5	15.2
1941	2,204,903	308,524	27,034	5,244	12.3	17.0
1940	2,067,953	292,446	26,620	4,817	12.9	16.5
1939	1,982,671	282,917	26,491	4,769	13.4	16.9
1938	2,005,955	281,007	26,905	4,677	13.4	16.6
1937	1,928,437	274,900	27,635	4,889	14.3	17.8
1936	1,881,883	262,907	27,786	4,666	14.8	17.7
1935	1,888,012	267,093	27,513	4,508	14.6	16.9
1934	1,866,231	301,405	28,480	5,322	15.3	17.7

Based on data from U. S. Bureau of the Census for continental United States.

TABLE 2b

NEONATAL MORTALITY FROM PREMATURE BIRTH, WHITE AND NON-WHITE; LOUISIANA, 1934-44*

Year	Number of live births		Deaths in the first month from premature birth			
			Number		Rate per 1,000 live births	
	White	Non-white	White	Non-white	White	Non-white
1944	37,463	23,587	441	416	11.8	17.6
1943	38,392	23,613	†	†	†	†
1942	35,082	23,011	†	†	†	†
1941	32,207	22,411	460	469	14.3	20.9
1940	29,853	21,063	408	445	13.7	21.1
1939	28,567	20,277	371	404	13.0	19.9
1938	28,684	20,183	454	437	15.8	21.7
1937	26,534	19,472	407	371	15.3	19.1
1936	25,376	18,452	396	377	15.6	20.4
1935	24,417	17,853	364	352	14.9	19.7
1934	24,877	18,126	340	376	13.7	20.7

*1934-40, by place of occurrence; 1941-44, by place of residence.
†Not available.
Based on data from U. S. Bureau of the Census.

These Census Bureau figures give evidence of decreased neonatal mortality from premature birth. Hospital fatality rates also offer some evidence that improved methods of diagnosis and treatment, as well as general care of these infants, have been effective in saving lives.

Table 3, showing the range in fatality rates of premature infants by birth-weight groups, is based on reports from 11 hospitals with 9,711 cases during varying periods from 1922 to 1940 and on reports from six hospitals with 5,126 cases during varying periods from 1940 to 1945. It can be seen that in all weight groups except the lowest, both lowest and highest rates were lower in the later than in the earlier period. These lowered rates were reported by hospitals in which some special efforts have been made to improve methods of care. In most hospitals the country over the fatality rates are not so favorable as those shown in this table.

TABLE 3

RANGE IN HOSPITAL FATALITY RATES IN EARLIER AND LATER PERIODS

Period	Fatality rate				
	Total 2,500 gm. or less	Less than 1,000 gm.	1,000-1,500 gm.	1,501-2,000 gm.	2,001-2,500 gm.
Earlier period (11 hospitals, 1922-40)	15.9-32.0	87.5-100.0	50.0-82.5	17.4-45.6	3.9-15.9
Later period (6 hospitals, 1940-45)	15.0-27.4	85.0-100.0	41.4-55.4	12.8-30.5	3.7-7.9

CAUSES OF DEATH AMONG PREMATURE INFANTS

Figure 3 shows the causes of neonatal deaths in the United States for 1944 and table 4 gives the corresponding information for Louisiana. Premature birth, as in every year, holds first place, accounting for almost half of these deaths. Some of these premature infants died because they were

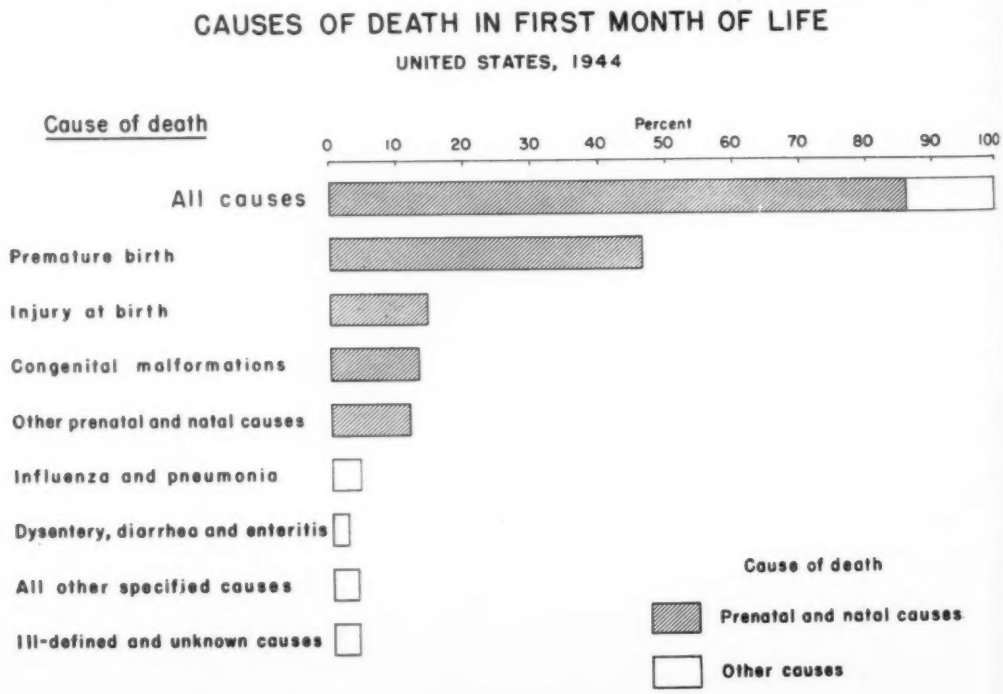

TABLE 4

CAUSES OF DEATH IN FIRST MONTH OF LIFE: LOUISIANA, 1944

Cause of death (Numbers in parenthesis are those of the International List of Causes of Death)	Number of deaths	Per cent distribution	Rate per 1,000 live births
All causes	1,654	100.0	27.1
Premature birth (159)	857	51.8	14.0
Injury at birth (160)	217	13.1	3.6
Congenital malformations (157)	119	7.2	1.9
Other prenatal and natal causes	210	12.7	3.4
Congenital debility (158)	27	1.6	0.4
Other diseases peculiar to the first year of life (161)*	149	9.0	2.4
Syphilis (30)	34	2.1	0.6
Influenza and pneumonia (33, 107-109)	88	5.3	1.4
Dysentery, diarrhea and enteritis (27, 119)	24	1.5	0.4
All other specified causes	92	5.6	1.5
Ill-defined and unknown causes (199, 200)	47	2.8	0.8

*That occurred in the first month.

Based on data from U. S. Bureau of the Census (Louisiana Summary of Vital Statistics 1944).

too immature for extra-uterine existence. Some died because of conditions associated with birth; anoxia, birth trauma, or congenital malformations not diagnosed. Some died because they received inadequate care: that is, they were unnecessarily exposed to infections, lived under unsuitable environmental conditions, were improperly fed, or were improperly or inadequately treated when they became ill.

An indication of the relative importance of the various causes of death of premature infants is obtained from study of the proportion of these infants that died at various ages. The data for the United States and for Louisiana in 1944 are shown in table 5.

TABLE 5

NEONATAL MORTALITY FROM PREMATURE BIRTH, BY AGE: UNITED STATES AND LOUISIANA, 1944

	United States		Louisiana	
Age at death	Number of deaths	Per cent	Number of deaths	Per cent
Under one month	32,065	100.0	857	100.0
Under one day	18,909	59.0	477	55.7
One day to six days	9,750	30.4	237	27.6
One week to three weeks	3,406	10.6	143	16.7

More than half of the deaths of premature infants occurred on the first day both in the United States as a whole and in Louisiana. These deaths can be reduced: (1) by the use of analgesics and anesthetics for women in labor that will not result in fetal anoxia; (2) by methods of resuscitation suitable to these small delicate infants; (3) by conservation of the infants' body heat and administration of oxygen.

Both in the country as a whole and in Louisiana more than one-fourth of the deaths occurred from the second to the seventh day. These deaths can be reduced by providing: (1) skilled medical and nursing care; (2) suitable environmental conditions—temperature, humidity, ventilation, increased oxygen, and protection from infection; (3) suitable feeding and fluids; and (4) appropriate treatment for diseases peculiar to these first days of life.

In the third period, from the end of the first week to the end of the first month, occurred only 11 per cent of the deaths in

the United States but 17 per cent of those in Louisiana. Deaths in this period are due largely to infection, and these are preventable.

The proportion of deaths of premature infants that occur between the end of the neonatal period and the end of the first year is very small.

In addition to improvement in methods for the diagnosis and treatment of abnormal conditions in the infants, *prevention* of premature labor or prolongation of pregnancy until the fetus weighs at least 1,500 gm. (always with consideration of the mother's welfare, of course) will do much to reduce morbidity and mortality from premature birth.

INCIDENCE AND PREVENTION OF PREMATURE BIRTH

Adequate prenatal care plays an important role both in the incidence of premature birth and in the proportion of premature infants who die. Parmelee[2] has shown that in a large series of hospital maternity cases only 5.2 per cent of the infants were premature among the mothers who were healthy, but 8.4 per cent were premature among the mothers who had medical complications. Of the infants of healthy mothers only 1.8 per cent died, compared with 3.5 per cent of the infants of mothers with complications.

Beck[3] has given careful consideration to this aspect of prevention of prematurity. He found, for example, that although for some women with cardiac conditions, pregnancy should not be risked, others may be brought safely to term with proper treatment. He stresses the importance of cardiologic consultation service through pregnancy for these cases. The danger of heart failure is greatest in the eighth month of pregnancy, according to Carr and Hamilton.[4] White[5] has found in her studies of diabetic women that premature births were reduced from 40 to 15 per cent when treatment to correct hormonal imbalance (estrogen and progesterone) was combined with insulin therapy.

Syphilis is known to be a cause of premature birth, and in these cases premature birth is preventable by early and adequate treatment of the mother.

In regard to *obstetric complications* of pregnancy, Anderson, Brown, and Lyon[6] have shown that statistically certain obstetric complications such as toxemia are not *per se* causes of premature labor, but antepartum bleeding was definitely associated with low birth weight. However, in comparing the incidence of each complication in mothers of mature infants and in mothers of premature infants, the authors did not take into consideration in this preliminary report either the severity of the complication or its relation to induced labor. Obviously when labor is induced or operative delivery is undertaken prematurely to save the mother's life, the complication must be considered the cause of the premature birth. As is brought out by Beck,[3] severe toxemia and eclampsia, with which premature birth is most frequently associated, usually do not occur when early and adequate prenatal care is given with due regard to the mother's diet and rest.

There are, unfortunately, a fairly large proportion of premature births for which no cause is determined. In this category such factors as poor nutrition, overwork, emotional disturbances, and so forth, may play a role. Information is scanty because medical histories do not usually record such items. A number of statistical studies of the quality of maternal diet in relation to the incidence of premature birth have shown that the incidence is highest when the diet is poor; lowest when the diet is "good." The incidence of prematurity has been found to be related also to economic status. It is higher among negroes than among whites and higher among hospital ward patients than among private patients. These differences may be related, of course, to poorer environmental conditions, poorer diets, harder work, and more illness among the lower than among the higher economic groups.

PROGNOSIS

Finally the evidence must be weighed not only as to the premature infant's chances of

survival but as to his chances for normal growth and development.

Speaking in terms of survival rates rather than fatality rates, table 6 shows the expected survival rates based on a mean between the low and the high rates reported (1940-1945) by five hospitals, giving a better than average grade of care. It can be seen that in the birth-weight group less than 1,000 gm. only a small proportion of the infants can be expected to survive. In the highest birth-weight group (2,001-2-500 gm.) 94 per cent should be expected to survive. It is particularly significant that the survival rate is so high in the two intermediate groups (52 and 78 per cent respectively).

TABLE 6

PREMATURE INFANTS: FATALITY AND SURVIVAL RATES; 5 HOSPITALS—4,737 CASES

Birth weight	Fatality rate		
gm.	Lowest	Highest	Estimated survival rate
Less than 1,000	85.0	100.0	8.0
1,000 - 1,500	41.4	55.4	52.0
1,501 - 2,000	12.8	30.5	78.0
2,001 - 2,500	3.7	7.9	94.0
Total	15.0	27.4	79.0

Data on physical growth, compiled on measurements of North American premature infants, are meager and not entirely satisfactory, particularly for infants in the lowest birth-weight group. Studies of growth in the first few months of life confirm the findings in earlier European studies that the fetal rate of growth is not interfered with by birth except temporarily. The rate of growth is greater the more immature the infant. Comparisons of weight and height of premature with mature infants must be corrected for conceptional age.

In regard to later growth the studies of Mohr and Bartelme[7] made in Hess' clinic in Chicago, show that the premature infant tends to catch up in weight and length with his siblings at some time near the end of the first to the fourth year or later depending on the degree of prematurity.

In regard to mental development of the premature infant, the studies of Mohr and Bartelme[7] based on relatively large numbers of premature infants and those of Gesell[8] based on long-term studies of individual infants show that premature infants who do not suffer from intracranial injury compare favorably with full-term infants. Mohr and Bartelme[7] found that "those children whose birth weight was low apparently developed mentally equally as well as those of heavier birth weight." Mental development also must be correlated with conceptional rather than chronologic age up to the time at which the premature infant attains maturity.

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HOARSENESS*

ITS POSSIBLE IMPLICATIONS AND ITS PROPER MANAGEMENT

GEORGE J. TAQUINO, M. D.†
NEW ORLEANS

One morning recently, at an otolaryngologic operative clinic at Charity Hospital

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†From the Department of Otolaryngology of the School of Medicine of Louisiana State University.

of Louisiana at New Orleans, four patients were seen with possible carcinoma of the larynx. Biopsy was positive in three of the four cases. In all three of the positive cases the disease was inoperable. In all four cases the patient's history included the statement that some time before—usually a fairly long time before—there had occurred some alteration in his voice to which he had paid no attention.

It must be granted that the striking combination of circumstances just decribed is not usual. One seldom sees in the course of a few hours three patients with proved carcinoma of the larynx. But the rest of the story is not at all unusual. It is, in fact, a sad commonplace. Hoarseness is almost always the first symptom of carcinoma of the larynx. Hoarseness is almost always ignored by the patient for longer or shorter periods of time. In too many instances, if he does seek medical advice, hoarseness, which is a symptom only, is treated as if it were a disease. And the end-result is that most patients with carcinoma of the larynx are beyond salvage when they are first seen by the otolaryngologist.

If proof of these statements is needed, statistics from the New Orleans Charity Hospital supply it. Carcinoma of the larynx begins in perhaps 80 per cent of all cases on the anterior half of the vocal cord. In this location it promptly interferes with approximation or vibration of the cord and disturbances of the voice occur correspondingly promptly. The majority of malignant neoplasms of the larynx are squamous-cell and therefore slow-growing. Metastases occur late because lymphatic drainage of the anterior half of the larynx is scanty. The circumstances in carcinoma of the larynx are thus highly favorable for cure, and complete removal of the growth with a margin of healthy tissue is possible in most cases which are seen early. Yet at the New Orleans Charity Hospital, over the two year period ending June 30, 1946, 13 tracheotomies were performed in carcinoma of the larynx, against no laryngectomies and laryngofissures. In the face of these proportions it is scarcely necessary to dwell further on the gloomy picture of this disease in an indigent hospital population, though it might be well to add that the experience in private practice is often almost equally gloomy. It also seems unnecessary to offer an apology, or even to present an explanation, for these remarks on hoarseness.

ETIOLOGIC CONSIDERATIONS

How important a symptom hoarseness may be is evident in the recent comprehensive article by Frank.[1] Defining hoarseness as any alteration in the speaking voice which gives it a rough or rasping character —a definition in which we concur—he lists 12 separate categories and 96 separate diseases and conditions which may give rise to it. The list, on the surface, is very complete. Whoever reads it, however, could with very little effort add several other etiologic possibilities.

Hoarseness may be the residuum, in colloquial language the hangover of a common cold. It may be the first symptom of an extrinsic and potentially serious condition such as aneurysm of the aorta or the subclavian artery, or a tumor of the pons or medulla, or the so-called syndrome of the jugular foramen. These conditions are admittedly unusual, but any one of them may occur, as any other rare disease may occur, in the case immediately under consideration, and they should always be borne in mind as possibilities. In fact, an experienced otolaryngologist could do worse than keep Frank's comprehensive list under the glass on his desk, while the general practitioner, to whom this plea is chiefly addressed, would profit even more greatly by the reminder.

To speak generally, hoarseness usually occurs under certain special circumstances which may be roughly classified as: (1) voice strain; (2) acute inflammatory and infectious conditions: (3) tuberculosis; (4) syphilis; and (5) neoplasms.

Most of these conditions need no special discussion, though a word or two of comment will perhaps be useful about certain of them. Voice strain, for instance, is not limited to singers, public speakers, teachers,

auctioneers and street hawkers. It also occurs in persons in constant association with deaf persons who do not use hearing aids. Children or adolescents suffering from hoarseness ought to be questioned about their attendance at football games and similar sports, where misuse of the voice is almost contagious. Even an adult who habitually attends baseball games sometimes provides the clue to his own disability when he contributes that information: There are such things as screamer's nodes as well as singer's nodes.

In this connection it might be mentioned that laryngeal neurosis, which may be evidenced by hoarseness as well as aphonia, is a definite clinical entity. Numerous instances of it were observed during the war, and Greene, in a discussion of Orton's[2] communication, recalled that in France and England during the 1938 Munich crisis, the almost epidemic hoarseness observed in many patients came to be known as "Munich sore throat" and was proved to be on a non-organic basis.

Not a great deal need be said about acute laryngeal conditions. Fever, malaise, rapid pulse, exanthemata, an elevated blood count and other systemic manifestations provide clues which are difficult to overlook. The warning is perhaps wise that diphtheria is always a possible diagnosis until it is adequately excluded; the disease still occurs and hoarseness is sometimes a first symptom.

This leaves us, then, with three conditions of extreme importance as the underlying causes of hoarseness, namely, tuberculosis, syphilis, and neoplasms, chiefly of the malignant variety. Whether or not tuberculosis is ever primary in the larynx is not a matter of great importance. The important consideration is that it is usually associated with pulmonary tuberculosis, that it is sometimes the first manifestation of an obscure and unsuspected thoracic disease, and that involvement of the larynx materially increases the risk of the pulmonary disease. In my personal experience laryngeal tuberculosis has invaribly been associated with pulmonary tuberculosis. The latter disease must therefore always be excluded in all cases of hoarseness, while laryngeal involvement must always be sought for in all cases of the pulmonary disease.

Hoarseness may be the first symptom to call attention to the presence of systemic syphilis. More often it is part of the general picture. Chancre is most unusual, but secondary and tertiary manifestations are not infrequent. The recurrent laryngeal nerve may be affected as part of the local process, as part of syphilis of the central nervous system, or as the result of pressure by an aneurysm or by a gumma of the mediastinum.

Benign neoplasms of the larynx are frequently responsible for persistent hoarseness. Papillomas are the most common variety, especially in children, but fibromas, myomas, lipomas, chondromas and cysts, especially of the epiglottis, may also occur. They are usually evident on proper examination. Papillomas may show a tendency to recurrence, even after adequate removal, until the young patients in whom they are most often seen outgrow them.

Malignant tumors of the larynx, as has already been intimated, are the most serious of the underlying causes of hoarseness, though, if they are recognized promptly, there is no cause for pessimism. The thing to be borne in mind about them, as well as about tuberculosis and syphilis, is that differential diagnosis is of vital importance, vital being used in its elementary significance—pertaining to life. The treatment of all three diseases is essentially different. The patient's life may be put in jeopardy if tuberculosis or syphilis is not recognized and if proper treatment is not promptly applied. His death warrant is signed if there is delay in the recognition of carcinoma. With the other two diseases it may be possible to recover lost ground. With malignancy it is never possible.

DIAGNOSTIC MEASURES

A discussion of diagnosis in a patient whose presenting symptom is hoarseness could well begin with the statement that the physician who makes such a diagnosis as

chronic laryngitis or laryngeal neurosis takes upon himself a heavy responsibility unless he has excluded every other possible cause of alteration in the voice. There is one peculiarly fortunate consideration about hoarseness. It points directly toward the structure, the larynx, which gives rise to the symptom. That consideration, on the other hand, may be disastrous rather than fortunate if the physician shuts his mind as to what it may imply and, in particular, if he fails to remember that even though the symptom arises in the larynx, the disease which causes it may lie at a considerable distance from that organ. The physician who fails to bear that fact in mind is the physician who treats a patient for hoarseness without proper investigation and who compounds the error by using local measures.

It is a safe rule that any hoarseness which has lasted more than two weeks demands investigation, which means considerably more than looking into the throat. An adequate study should include.

1. A complete history, including an inquiry into the patient's habits, use of tobacco and alcohol, occupation, and occupational environment, with particular respect to dust, smoke and gases.
2. A complete physical examination.
3. Indirect laryngoscopy.
4. Laboratory studies, including urinalysis, blood studies, blood serology, metabolic tests, and roentgenologic examination of the chest and sinuses.
5. Direct laryngoscopy, bronchoscopy or esophagoscopy, according to the indications in the special case.
6. Biopsy.

Certain points in this diagnostic regimen need special comment. It should be emphasized that while very few practitioners who are not specialists in otolaryngology are able to make a satisfactory examination of the larynx by mirrors, there is no reason why every practitioner should not train himself to do so. It is not the responsibility of the physician who is not a specialist to make a differential diagnosis. It is definitely his responsibility to know the normal, so that he can recognize deviations from it and can refer the patient to a qualified specialist for such additional examinations as may be necessary.

Another point to be emphasized in indirect laryngoscopy is that the examination is not satisfactory unless there is a full view of the entire larynx and anterior commissure. Jackson's[3] warning should be remembered, that death lurks behind an overhanging epiglottis. If the desired view is not possible for this or any other reason, the patient should at once be referred for direct laryngoscopy, which is a hospital procedure, not an office method. Indirect laryngoscopy, however, is satisfactory and adequate in a very large proportion of cases. With patience it can be carried out even on a child. Without patience it is difficult to carry out even on an adult.

Special examinations should not be unduly delayed, the patient himself is likely already to have delayed too long. Damitz and Dill,[4] in an interesting analysis of 300 consecutive cases of hoarseness at the Henry Ford Hospital, found that the duration of hoarseness before the patients were seen ranged from eight and a half weeks in chronic non-specific laryngitis, to two weeks in benign neoplasms. In malignancy the duration was nine and a half months.

Biopsy is the definitive step of differential diagnosis. Without it a conclusive diagnosis is not possible, and upon its outcome depends the form of therapy to be followed in the special case. The specimen is usually small and the safety of the patient demands that it be passed upon by a well qualified pathologist.

THERAPY

Not a great deal need be said about therapy in a presentation on hoarseness, and what is said here is chiefly in the way of warning. The fundamental point has already been made, that the symptom must not be treated. Instead, the disease is treated when the etiology of the symptom has been established.

The first principle of treatment, regardless of the underlying disease, is absolute prohibition of the use of the voice. The

common advice to the patient to whisper if there is something important to be said is incorrect. A whisper causes more trauma to the larynx than does the full speaking voice. Almost the only exception to the rule that the voice should be completely rested is in laryngeal neurosis, in which rest only makes a bad matter worse.

General hygienic measures are important. If the patient works in an unfavorable environment, he should, preferably, change his occupation. Failing that, he should spend as much time as possible in the fresh air. Tobacco and alcohol are not permitted.

Local applications are seldom of value. Steam inhalations are useful in acute conditions, though moisture, rather than heat or any special drug, is responsible for whatever effects may be achieved. Expectorant mixtures are useful in conditions in which they are indicated. Opiates and their derivatives, which destroy the cough reflex—an overlooked form of therapy—should be avoided; they are extremely dangerous. Atropine, which dries up secretions, is also contraindicated. All measures of this kind sacrifice the ultimate good for temporary comfort.

When the basic cause of hoarseness is some systemic condition, treatment is the business of the appropriate specialist, who is not the otolaryngologist. It is particularly important in tuberculosis that management be in the hands of an experienced phthisiologist. Syphilis also demands expert care. If diphtheria is suspected as a possible cause of hoarseness, antitoxin should be given at once, in full doses. Laboratory confirmation is necessary for a final diagnosis, but delay in therapy may be fatal.

Hoarseness due to neoplasms, or, to state it more correctly, neoplasms of the larynx which give rise to hoarseness, are treated by local incision if they are benign, by laryngofissure, laryngectomy, or, in the occasional carefully selected case, by irradiation, if they are malignant. In late cases the only procedure is palliative, and it may fairly be said that every case in which tracheotomy is employed is one more illustration of the danger of delaying a complete investigation of hoarseness.

SUMMARY AND CONCLUSIONS

1. Hoarseness is a symptom, the presence of which, for longer than two weeks, demands a thorough investigation. It may arise from a variety of causes, of which tuberculosis, syphilis and carcinoma of the larynx are the most important.

2. The business of the physician who is confronted with a patient complaining of hoarseness is not to treat the symptom but to diagnose the disease which gives rise to it.

3. The routine of investigation is described, and it is emphasized that biopsy should not be omitted in any case in which the diagnosis is not absolutely clear without it.

4. The general practitioner carries a heavy responsibility in the diagnosis of the causes of hoarseness, since he so often sees the patient first. He can readily train himself to perform indirect laryngoscopy. His function is not to make a differential diagnosis, but to recognize deviatons from the normal, so that the patient can be referred to a specialist for appropriate further study.

5. Education of the lay public as to the possible implications of hoarseness is an essential phase of all cancer educational campaigns.

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DISCUSSION

Dr. W. A. Wagner (New Orleans): Dr. Taquino has brought forth something that is timely. I think that all of us larygologists have seen malignancies late and when I say late perhaps I should emphasize that *too late.* I saw a malignancy recently—a patient who had been under treatment for better than six months by his family physician. Now he presents an inoperable malignancy of the larynx. If it were not for the fact that he developed the

mass in the upper clavicular region that did not precede but followed masses up along the upper cervical line of lymph node, he perhaps would not have been in to see me, but because of the mass which occurred the doctor thought there was some cause in the throat. There is no reason for that. I think that the general practitioner should be cautioned just as Dr. Taquino has done, that the early sign of malignancy of the larynx is hoarseness and when you wait for masses or other signs and symptoms you are going to have types of lesions that we, who are able to handle them properly, must resort to palliation. Palliation is all right and has been all right perhaps years ago, but today nobody should ask for palliation of a malignancy of the larynx when we are able today properly to handle malignancies of the larynx. It is true, as Dr. Taquino well brought the point out, that hoarseness is not the only sign of malignancy nor is hoarseness always indicative of malignancy. We see many lesions that are producing hoarseness that are non-malignant but unless the doctor—and I say the doctor, the general practitioner, is conscious of the variety of causes of hoarseness then only will we be able to get these patients early. If he is not we will not be able to save them; even though radiology has contributed much in the treatment of malignancy it has fallen short and when I say fallen short I mean that. We can read all the wonderful results by such men as Cutler and others who have had a tremendous experience with x-ray therapy but if we are going to resort to x-ray therapy to save all malignancies of the larynx we are going to fall short just like the radiologist with his x-ray apparatus. Irradiation does have merit, but early malignancy—and I feel sure of this when I speak these words—because I am merely quoting authorities—that those early malignancies are better treated by surgical intervention than by irradiation.

Dr. Taquino should be complimented and this thought should be conveyed to the general practitioner not just this time but time and time again.

Dr. Joseph Stamm (New Orleans): I would like to ask one question. Would Dr. Taquino briefly tell us how he would handle leukoplakia?

Dr. Taquino (in closing): I would like to emphasize one point. Surgery can not be replaced by x-ray therapy. Surgery is the ideal thing to do when dealing with a malignant growth. I think results from operation are so far superior that one ought not to consider other therapy except in cases where it is a physical impossibility to do an operation. I have a patient on whom I have just done a tracheotomy five days ago. The man walked in the office. He had refused to see doctors. He has definitely got a carcinoma of the larynx. I did a tracheotomy on him—he has mediastinal involvement, so there was nothing to do but palliative treatment. How much good it will be I do not know. He will probably get along just as well with tracheotomy as with x-ray therapy.

In school, I teach all of my students to become familiar with the use of the laryngeal mirror, thus being able to recognize a normal larynx from an abnormal one. The student should be able to differentiate between a normal and abnormal condition, so when the abnormal one presents itself he should be able to recognize it immediately and see that the patient is placed in the proper hands.

I also tell them when an abnormality appears to ask themselves the question,—Am I dealing with a cancer, and then prove whether or not it is present and be sure also that you prove the diagnosis before advising the patient that he has or has not a cancer; do not make any rash statements or use rash judgment in the treatment of the patient.

NEW ORLEANS

Medical and Surgical Journal

Established 1844

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1430 Tulane Avenue

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THE JOURNAL *does not hold itself responsible for statements made by any contributor.*

SOUTHERN REGIONAL CONFERENCE

The Council on Medical Service of the A.M.A. is sponsoring a Southern Regional Conference to be held at the Roosevelt Hotel in New Orleans Thursday and Friday, October 23-24. This conference will include representatives from the States of Texas, Oklahoma, Arkansas, Mississippi, Alabama and Louisiana. The purpose of the meeting is to discuss certain problems of these various states: Liaison Between the A.M.A. and the Component Medical Societies; The Washington Legislative Picture; Medical Society Public Relations; Prepayment Medical and Surgical Care Plan Problems; Industrial Health Problems of the South; and Rural Health Problems.

The President-elect of the A.M.A., Dr. R. L. Sensenich has tentatively agreed to address the meeting and addresses of welcome will be made by Dr. Gilbert C. Anderson, President of the Louisiana State Medical Society and Dr. H. Ashton Thomas, President of the Orleans Parish Medical Society.

The meeting is being held under the chairmanship of Dr. James R. McVay of the national organization and Dr. A. V. Friedrichs of the State Society. The Louisiana State University Medical School and the Tulane University School of Medicine have been invited to send representatives to this conference. All physicians who may be interested in these problems are also invited to attend.

A full program may be found on pages 134, 135 of this issue of the Journal.

KALA-AZAR IN LOUISIANA

The recent report by H. D. Ecker and J. M. Lubitz of two cases of visceral leishmaniasis in Louisiana should sharpen the suspicions of physicians concerning the possibility of kala-azar in patients complaining of symptoms or signs consistent with this disorder. This is particularly true now because of the increase in amount and rapidity of world travel and especially because of the return of great numbers of veterans from endemic areas. In view of the fact that the incubation period may exceed one year, infected individuals may be discharged from the Services in apparently good physical condition. Obviously such

possibility will exist months after the withdrawal of the last of our armed forces.

The diagnosis may be suspected in patients with fever, weight loss, anemia, leukopenia, abnormal proteins and enlarged liver and spleen. Confirmation depends on the identification of the Leishman-Donovan bodies by means of culture, blood or tissue examination. It is recommended that repeated sternal marrow studies be done before resorting to the more hazardous liver and splenic punctures for the parasite occurs in groups or colonies and one or more marrow smears may yield negative results even in the hands of experienced examiners.

Treatment with pentavalent antimony compounds or stilbamidine is highly effective. Stilbamidine offers hope of cure in those instances which fail to respond to the pentavalent antimoniols. Toxicity with any of these drugs is low when proper precautions of administration are observed.

Drs. Ecker and Lubitz are to be commended on their clinical acumen in recognizing and successfully treating the first two cases of kala-azar in Louisiana.

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THE DIAGNOSIS OF MALARIA

Inquiry made at the Louisiana State Charity Hospital in New Orleans has revealed that no cases of malaria endemic to Louisiana have been treated in the past three years. Further, patients sent in to Charity Hospital with a diagnosis of malaria have proved to be suffering from other febrile disorders in very many instances. Thus, most of the malaria present in our state is treated by country practitioners. These busy men will welcome the improvements made in the technic of staining plasmodia. Thick films are not made as thick as formerly. The amount of blood, 2 to 4 small drops, is spread, not stirred, with a clean wooden applicator, match or glass rod, so that when the slide is turned vertically the blood does not immediately form a definite drop at the dependent point; instead of flowing quickly it should appear to crawl. The slide is then placed flat and allowed to dry. Each slide should bear some identification mark. Walker's method of staining with Giemsa Blue which demonstrates the malarial parasites most beautifully is as follows:

Dip for one second in methylene blue-phosphate solution.[1]

Wash gently in distilled water to remove excess blue solution.

Place *face downward* on a curved staining plate in diluted Giemsa stain[2] for eight to ten minutes (1 drop to each cubic centimeter of buffer water[3]).

Drain and dry thoroughly with gentle heat.

Examine under oil immersion. The *margin* of the thick film *usually shows better color differentiation than does the center.*

Note the absence of red blood cells, the rich blue-violet color of the nuclei of leukocytes, the red-violet dark cytoplasmic granules of polymorphonuclears, the coppery-red eosinophilic granules, groups of pale violet platelets. The morphology of leukocytes is well preserved. Each parasite consists of one or more masses of reddish chromatin closely associated with a variable amount of greenish blue cytoplasm. Pigment may be recognized in the larger parasites. Parasites are easily distinguished from ruptured leukocytes, platelets, bacteria, spores and other artefacts. Many bacteria are present in blood from punctures of skin and are ignored.

Physicians interested may obtain these solutions at a very nominal cost from Dr. A. J. Walker of the Department of Tropical Medicine at Tulane University School of Medicine.

1. *Methylene blue-phosphate*
   Methylene blue ..... 0.5 Gm.
   Disodium monohydrogen phosphate, anhydrous (Na_2HPO_4) 1.5 Gm.
   Monopotassium dihydrogen phosphate (KH_2PO_4 ..... 0.5 Gm.
   Distilled water..... 400 cc.
   Filter before use; avoid evaporation.
2. *Giemsa Stain*: any well known brand (certified) in liquid form or:—Giesma powdered stain (certified) ..... 0.75 Gm.
   Pure methyl alcohol..... 65 cc.

Pure glycerine ..... 35 cc.
Shake well in bottle with glass beads and *keep tightly stoppered at all times.* Use from 30 cc. or 60 cc. bottles.

3. *Buffer Water*
Disodium monohydrogen phosphate anhydrous ..... 7 parts
Monopotassium dihydrogen phosphate ..... 4 parts
Mix thoroughly in a mortar. Add 2.0 Gm. to 1000 cc. distilled water. Renew if slightly cloudy.

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ORGANIZATION SECTION

The Executive Committee dedicates this section to the members of the Louisiana State Medical Society, feeling that a proper discussion of salient issues will contribute to the understanding and fortification of our Society.

An informed profession should be a wise one.

VETERANS ADMINISTRATION AGREEMENT FOR MEDICAL CARE OF VETERANS

In December, 1946 the Louisiana State Medical Society entered into an agreement with the Veterans Administration for medical care of veterans with service connected disabilities. The object of this agreement was to furnish for veterans medical care by the physicians in their home town and obviate the necessity of going to another locality for service.

During the past months since the contract has been in effect there have been some complaints concerning the operation of this agreement. In order that an appropriate investigation may be made concerning inadequacies of the plan it is requested that comment be furnished by members of the State Society concerning their experience with this project. In submitting such information it is desired that full facts in connection with specific cases be given. The data will be compiled and an effort will be made to have all discrepancies clarified.

Further information will be carried in future issues of the Journal.

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SOUTHERN REGIONAL CONFERENCE OF AMA TO BE HELD IN NEW ORLEANS IN OCTOBER

The Southern Regional Conference sponsored by the Council on Medical Service of the American Medical Association will be held in New Orleans at the Roosevelt Hotel on Thursday, October 23, and Friday, October 24. Arrangements for the conference are being handled by the Council on Medical Service and Public Relations of the Louisiana State Medical Society. Dr. A. V. Friedrichs is chairman of the arrangements.

The States of Alabama, Mississippi, Texas, Oklahoma, Arkansas, Tennessee, and Louisiana will participate in the conference. Committees invited to attend the conference from the mentioned State Societies are: Public Relations Committee, Prepayment Medical and Surgical Care Plan Committee, Industrial Health Committee, Rural Health Committee and officers and directors of the various state and county (parish) medical societies in the South.

While the conference is primarily a meeting of the officers, directors, and committees of the various State Societies in the South, any doctor interested in the meeting is invited to attend. The meeting is open to all physicians, particularly those interested in the expansion of medical care in industrial and rural areas.

Numerous distinguished guests from the American Medical Association are scheduled to appear on the program together with many well known representatives from the various states.

The meeting will be opened by Addresses of Welcome by Dr. Gilbert C. Anderson, President, Louisiana State Medical Society, and Dr. H. Ashton Thomas, President of the Orleans Parish Medical Society. American Medical Association representatives scheduled to appear on the program on Thursday, October 23, are Dr. James R.

McVay, Chairman of the Council on Medical Service of the AMA, Dr. George F. Lull, Secretary and General Manager of the AMA, and Dr. Joseph S. Lawrence, Director of the Washington Office of the Council on Medical Service of the AMA.

The subject "What is Good Medical Society Public Relations" will be discussed on Thursday morning with Henry S. Johnson, Director of Public Relations of the Medical Society of Virginia, as Moderator.

The afternoon session of the Thursday program has been devoted to a discussion of "Prepayment Medical and Surgical Care Plan Problems".

The program on Friday morning, October 24,. will be devoted to "Industrial Health Problems of the South", with Dr. Stanley J. Seeger, Chairman of the Council on Industrial Health of the AMA, as Moderator.

"Rural Health Problems" will be the topic for discussion on Friday afternoon. Dr. J. Paul Jones of Camden, Alabama, of the Committee on Rural Medical Service of the AMA, will be the Moderator at this session.

Each morning and afternoon session will have panel discussants to lead the discussion of the problems and everyone in attendance may participate actively in the discussions.

A cocktail party has been scheduled for Thursday evening, 5 to 7 p. m. in the Roosevelt Hotel. The party is scheduled with the object of offering an opportunity to members of the State Society to meet the visiting guests from the AMA and other State Societies.

Following is a copy of the tentative program as announced by the Council on Medical Service of the AMA.

A TENTATIVE PROGRAM
For
THE SOUTHERN REGIONAL CONFERENCE
Roosevelt Hotel, October 23-24
New Orleans, La.
Chairman—James R. McVay, M. D., Chairman
Council on Medical Service
American Medical Association

THURSDAY, OCTOBER 23

9:00 a. m.—Registration

9:30 a. m.—Address of Welcome
Gilbert C. Anderson, M. D., President, Louisiana State Medical Society
H. Ashton Thomas, M. D., President, Orleans Parish Medical Society

9:45 a. m.—Purpose of Meeting
James R. McVay, M. D.

10:00 a. m.—Liaison between AMA and the Component Medical Societies, George F. Lull, M. D., Secretary and General Manager, AMA

10:30 a. m.—The Washington Legislative Picture
Joseph S. Lawrence, M. D., Director, Washington Office of the Council on Medical Service of the AMA
What is Good Medical Society Public Relations?

11:00 a. m.—Public Relations Round Table Discussion
Moderator—Henry S. Johnson, Director of Public Relations, Medical Society of Virginia
Panel Discussants—
A. V. Friedrichs, M. D., Chairman, Council on Medical Service and Public Relations, Louisiana State Medical Society
Donovan C. Browne, M. D., Chairman, Public Relations Committee, Orleans Parish Medical Society
Richard Graham, Executive Secretary, Oklahoma State Medical Association
W. R. Brooksher, M. D., Secretary, Arkansas Medical Society
Holman Taylor, M. D., Secretary, State Medical Association of Texas

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1:00 p. m.—Luncheon (Dutch)

THURSDAY, OCTOBER 23
Afternoon Session

2:30 p. m.—*Prepayment Medical and Surgical Care Plan Problems*
Prepayment Medical and Surgical Care Plan Round Table Discussion
Moderator—Charles R. Henry, M. D., Chairman Committee on Medical Service and Public Relations, Arkansas Medical Society, Little Rock, Arkansas
Panel Discussants—
O. B. Owens, M. D., President, Louisiana Physicians Service, Alexandria, Louisiana
W. R. McBee, Executive Director, Group Medical and Surgical Service, Dallas, Texas

Ed S. Moore, Manager, Hospital Service Corporation of Alabama, Birmingham, Alabama
Edward F. Groner, Manager, Hospital Service Association of New Orleans, New Orleans, Louisiana
Report of States—
Alabama—Mississippi—Texas—Oklahoma—Arkansas—Tennessee—Louisiana

FRIDAY, OCTOBER 24
Morning Session

10:00 a. m.—*Industrial Health Problems of the South*
Industrial Health Round Table Discussion*
Moderator—Stanley J. Seeger, M. D., Chairman, Council on Industrial Health of the AMA
Panel Discussants—
Lloyd Noland, M. D., Medical Director, Tennessee Coal, Iron and R. R. Co., Fairfield, Alabama
J. T. Scott, Jr., M. D., Chairman, Committee on Industrial Health, Louisiana State Medical Society, New Orleans, Louisiana.
Carl Nau, M. D., Prof. of Physiology, Preventive Medicine and Public Health, University of Texas Medical School, Galveston
Jean Felton, M. D., Superintendent, Health Dept., Monsanto Chemical Company, Clinton Laboratories, P. O. Box 1991, Knoxville, Tenn.
O. M. Derryberry, M. D., Chief of Employee Health Services Division, Tennessee Valley Authority, Chattanooga, Tennessee

*The Industrial Health group will meet separately on Friday afternoon to discuss the technical problems of industrial programs.

12:15 p. m.—Luncheon (Dutch)

FRIDAY, OCTOBER 24
Afternoon Session

2:00 p. m.—*Rural Health Problems*
Rural Health Round Table Discussion
Moderator—J. Paul Jones, Camden, Alabama, Committee on Rural Medical Service, AMA
Panel Discussants—
Allen T. Stewart, M. D., Member National Committee on Rural Medical Service, Lubbock, Texas
Guy R. Jones, M. D., Chairman, State Society Committee on Rural Medical Service, Lockport, La.
Chairman, Mississippi Rural Health Committee
A. S. Buchanan, M. D., Prescott, Arkansas State Society Committee on Rural Medical Service

The preceding program is a tentative program and invitations have been extended to personnel listed thereon. However, final acceptance of their appearance on the program was not received when this article went to press.

TRANSACTIONS OF ORLEANS PARISH MEDICAL SOCIETY

Sept. 9. Orleans Parish Radiological Society, 7:30 p. m.
Sept. 15. Hotel Dieu Staff, 8 p. m.
Sept. 18. Clinico-pathologic Conference, Touro Infirmary, 12 noon.
Veterans Administration Hospital Staff, 8 p. m.
Sept. 19. Lakeshore Hospital Staff, 8 p. m.
Sept. 24. French Hospital Staff, 8 p. m.
Sept. 25. DePaul Sanitarium Staff, 8 p. m.
Sept. 26. New Orleans Dispensary for Women and Children Staff, 8 p. m.
Oct. 1. Mercy Hospital Staff, 8 p. m.
Oct. 2. Clinico-pathologic Conference, Touro Infirmary, 12 noon.
Executive Committee, Baptist Hospital, 8 p. m.
Oct. 3. Ochsner Clinic Staff, 8 p m.
Oct. 6. Board of Directors, Orleans Parish Medical Society, 8 p. m.
Oct. 7. Eye, Ear, Nose and Throat Staff, 8 p. m.
Oct. 8. Woman's Auxiliary, Orleans Club, 3 p. m.
Touro Infirmary Staff, 8 p. m.

NEWS ITEMS

Dr. Earl Conway Smith was elected president of the New Orleans Gynecological and Obstetrical Society at the annual meeting of this organization July 1. Other officers elected were: Dr. W. D. Beacham, president-elect; Dr. Curtis H. Tyrone, vice-president; Dr. John S. Herring, secretary; and Dr. Harry Meyer, treasurer.

Dr. G. J. von Langermann was recently elected recording secretary of the Altrusa Club of New Orleans.

Drs. W. D. Beacham, John W. Weed and B. Bernard Weinstein attended the meeting of the American Society for the study of Sterility in Atlantic City.

Dr. Weinstein presented a paper before the Society on the "Surgical Management of the Tubal Factor in Sterility", and presided over a meeting of the Research Correlating Committee of which he is chairman.

N. J. TESSITORE, Secy.

LOUISIANA STATE MEDICAL SOCIETY NEWS

CALENDAR

PARISH AND DISTRICT MEDICAL SOCIETY MEETINGS

Society	Date	Place
East Baton Rouge	Second Wednesday of every month	Baton Rouge
Morehouse	Second Tuesday of every month	Bastrop
Orleans	Second Monday of every month	New Orleans
Ouachita	First Thursday of very month	Monroe
Rapides	First Monday of every month	Alexandria
Sabine	First Wednesday of every month	
Second District	Third Thursday of every month	
Shreveport	First Tuesday of every month	Shreveport
Vernon	First Thursday of every month	

1948 ANNUAL MEETING

Following is personnel of Advisory Committee and list of chairmen of committees who have been appointed to handle the forthcoming meeting of the State Society in Monroe, April 12-14, 1948.

Advisory Committee: John G. Snelling, Chairman, A. Scott Hamilton, Co-Chairman, C. P. Gray, Sr., James Q. Graves, George Wright and DeWitt T. Milam.

Badges, Signs and Decorations: Dr. Wood Scott.

Banquet: Dr. C. P. Gray, Jr.

Budget and Finance: Dr. Henson Coon.

Commercial Exhibits: Dr. Clifford Johnson.

Entertainment: Dr. C. B. Flinn.

Golf: Dr. Fred Marx.

Hotel and Meeting Rooms: Dr. J. W. Cummins.

Lanterns and Sound Equipment: Dr. M. W. Hunter.

Luncheons: Dr. Henry Guerriero.

Program: Dr. Glenn Gallaspy.

Publicity: Dr. W. L. Bendel.

Registration: Dr. P. L. Perot.

Scientific Exhibits: Dr. J. E. Walsworth.

Transportation: Dr. George Varino.

JARRETT RESIGNS

Dr. Lewis E. Jarrett who has been director of Touro Infirmary since April 7, 1944 has resigned his position at this institution. Dr. Jarrett came to New Orleans from Richmond, Virginia. In his short stay in this city he has become very well liked and very popular. Last year he was elected president of the Louisiana Hospital Association. It is with considerable regret that the medical profession will see Dr. Jarrett leave the city.

NEW SCHOOL OF PREVENTIVE AND TROPICAL MEDICINE

Dr. Rufus C. Harris, president of the Tulane University has announced that the medical school is prepared to give a new course in the Department of Tropical Medicine and Public Health which will lead to a master's degree in public health (tropical medicine). All of the required courses that will lead to a master's degree in public health will be given, plus extra courses in tropical medicine. Preventive medicine and public health activties will be those that are given at the important schools of public health throughout the country but an addition of the electives in tropical medicine for certain required courses will qualify the man who wishes to practice in the tropics to be a well rounded public health officer as well as skilled in the field of tropical medicine.

AMERICAN HOSPITAL ASSOCIATION

The forty-ninth annual convention of the American Hospital Association will be held Monday, September 22-25, in St. Louis, Missouri. There will be an opening general session on the first day, following which the convention will be broken into four sections on Professional Practice, Administrative Practice, Hospital Planning and Plant Operation and Special Aspects of Hospital Administration. The final afternoon session will consist of a resumé of the discussion in all of the special sessions under the topic "American Hospitals Today".

AMERICAN ACADEMY OF GENERAL PRACTICE OF NEW ORLEANS

At an organization meeting of the American Academy of General Practice of New Orleans held on August 20, Dr. Joseph C. Menendez was elected president, Dr. F. A. Fatter, vice-president and Dr. R. E. Gillaspie, secretary-treasurer. Named to serve as members of the Board of Director sare Dr. E. L. Leckert, Dr. W. A. Gillaspie, Dr. Charles Moseley, Dr. Lucien C. Delery, Dr. Joseph J. Ciolino, Dr. Theo F. Kirn, Dr. N. J. Chetta, Dr. George Barnes and Dr. Frank Gallo. Dr. J. P. Sanders, of Shreveport, president of the American Academy of

General Practice of Louisiana and a representative on the Board of Directors of the national organization, addressed the group.

CONSTRUCTION OF V. A. HOSPITALS TO BE DELAYED

On account of the increasing cost of building of hospitals the V. A. hospital project necessarily will have to be considerably delayed. Large amounts of money have been voted for these hospitals but the cost has gone up so rapidly that the almost one billion dollars that is available will not begin to complete the program as outlined by General Bradley and Colonel Hardin.

The V. A. hospital which is to be built back of the Charity Hospital in New Orleans has already been started to a limited degree. The gas plant has been removed from the property, the ground has been cleared and the preliminary test piling has been initiated.

This delay is unfortunate as there is a very distinct need and want for the new institutions. It might be added that hospital costs have increased from 85 cents a cubic foot in 1945 to $1.25 in 1946, to $1.80 as of today.

POSTGRADUATE COURSES—AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians announces a series of courses in various phases of internal medicine. These courses are given in various portions of the country and are scheduled to run from September 1 until the middle of December. The detailed programs for the first five have been issued. The first is internal medicine at the University of Pittsburgh Medical Center and other Pittsburgh institutions from September 1-13. Course No. 2 is on psychosomatic medicine under the direction of Dr. F. G. Ebaugh and will be given at the University of Colorado Medical Center from September 8-20. Course No. 3, is on the mechanics of disease under the direction of Dr. George W. Thorn of Peter Bent Brigham Hospital where the course will be held for two weeks beginning September 15. Course No. 4 will be of a week's duration under the direction of Dr. W. B. Castle at various Boston institutions. The course will be devoted to subjects on hematology and blood disorders and will start October 13. Course No. 5 is likewise for one week and will be held under the auspices of the University of Pennsylvania Graduate School of Medicine with Dr. J. H. Comroe, Jr. acting as director. This course will be on the physiological basis for internal medicine and is scheduled to begin October 20.

Subsequent courses will be conducted at the Southwestern Medical College, Dallas, Texas, on cardiovascular disease; chemotherapy at the Boston University School of Medicine; internal medicine at the University of Wisconsin Medical School, Madison; at the Massachusetts General Hospital on recent advances in the diagnosis and treatment of cardiovascular disease; gastroenterology at the Graduate Hospital of the University of Pennsylvania; cardiology at the Yale University School of Medicine, and the last one that has been provided for is one in general medicine at the University of Texas School of Medicine.

These courses are open primarily to the Fellows and Associates of the American College of Physicians. In the event that within a period of three weeks before a course commences the minimal registration figures have not obtained, non-members may take the course. Minimal registration, depending on the institution and the course, is from 25 to 70. The fees vary from $60-$120 for members of the College and for non-members double the figures. Further information may be obtained from Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Pa.

LOUISIANA STATE SOCIETY OF MEDICAL TECHNOLOGISTS

The Louisiana State Society of Medical Technologists, in cooperation with the American Society of Medical Technologists will sponsor a four day seminar at Loyola University in New Orleans September 29-October 2, 1947. Registered medical technologists from Texas, Florida, Arkansas, Mississippi and Louisiana have been invited to attend and all interested doctors and students are invited to be guests. The program will consist of lectures and demonstrations on mycology and hematology to be given by outstanding medical men of New Orleans. Anyone planning to attend this seminar should notify Miss Dorothy Dickinson, Secretary of the Louisiana State Society of Medical Technologists, P. O. Box 1368, Alexandria.

MEETING MISSISSIPPI VALLEY MEDICAL SOCIETY

The 12th Annual Meeting of the Mississippi Valley Medical Society at Burlington, Iowa, Oct. 1-3, will have over 30 clinician-teacher speakers. Oct. 1 will feature an all-St. Louis program conducted by clinical teachers from St. Louis and Washington Universities. On Oct. 2 there will be speakers from various medical centers including Dr. E. L. Bortz, President, American Medical Ass'n., Dr. I. H. Neece, President, Illinois State Medical Society, Dr. M. B. Simpson, President, Missouri State Medical Assn., and Dr. H. A. Spilman, President, Iowa State Medical Society. There will be a social hour and banquet on this date. The afternoon program will be devoted to presentations by a group from the University of Iowa. Oct. 3 will feature an all-Chicago program with a number of well-known clinical teachers from Chicago medical schools. A Clinico-Pathologic Conference and a Round Table luncheon will be featured on this date.

THE EYE-BANK FOR SIGHT RESTORATION, INC.

An affiliated "Eye-Bank" has been organized in New Orleans, La., which will have the cooperation of the Louisiana State University Medical School and the Tulane University Medical School, it was announced here at national headquarters of The Eye-Bank for Sight Restoration, Inc. Other affiliated Eye-Banks are functioning in Boston and Chicago.

The new Eye-Bank is located in the Hutchinson Memorial Building, New Orleans, and Mrs. Orville Ewing is serving as Executive Director. The officers are Charles E. Fenner, President; Dr. William B. Clark, 1st Vice President; Dr. George L. Hardin, 2d Vice President; John F. Reilly, Treasurer; and John W. Sims, Secretary.

ACADEMY-INTERNATIONAL OF MEDICINE

This organization announces that as a service to the profession it is offering to mail, upon request, to any member of the Louisiana State Medical Society a complimentary copy of their medical and surgical film catalogue which contains a list of the films that are now available and the source from which they may be obtained by the borrower.

Requests for the catalogue should be sent to the Academy - International of Medicine, 214 West Sixth Street, Topeka, Kansas.

MICROFILM SERVICE STILL AVAILABLE

Through the microfilm service of the Army Medical Library, physicians, libraries and professional workers almost anywhere in the world may obtain facsimile replicas of the great bulk of existing medical literature on 35 millimeter film, according to Colonel J. H. McNinch, Commandant of the Army Medical Library.

Any page of a medical journal, book or manuscript is photographed with high-speed cameras in the microfilm process. The physician or researcher requesting the material receives the film reproduction reduced to the size of a large postage stamp for each page. These pages can be read either in small-size film reviewers which enlarge the tiny microfilm, or they can be projected to large, readable size in special machines now available in many libraries and research centers. A whole book on microfilm takes only as much space as the corner of a coat pocket.

Costs are moderate for the microfilm duplicating service that brings the world's medical literature into the office of any physician however remote. Articles in medical periodicals are duplicated on microfilm for fifty cents each. Books are duplicated for fifty cents for each fifty pages or fraction thereof. Photostats are priced at fifty cents for each ten pages or fraction thereof for any single volume. There are certain restrictions on photoduplication to protect the rights of copyright owners.

INDUSTRIAL HYGIENE DIVISION—FEDERAL SECURITY AGENCY

Formation of an Atomic Radiations Unit in the Chemical Section of the Industrial Hygiene Division, U. S. Public Health Service, was announced by Dr. J. G. Townsend, Chief of the Division. Duncan Holaday, Engineer (R), is in charge of the new Unit.

The new Unit will advise and assist State industrial hygiene units in detecting and evaluating health hazards produced by the use of radio-active isotopes and high energy machines such as x-ray machines and betatrons.

PHYSICIAN WANTED

The town of Vinton, Louisiana is in need of a physician. Population approximately 3,000. At present the nearest doctors are 15 miles east and 12 miles west of town. Equipment for sale by retiring physician. Contact Mrs. Jo McGann, Clerk, Town of Vinton.

HEALTH OF NEW ORLEANS

The Bureau of the Census, Department of Commerce, from the figures reported by the New Orleans Health Department announces that for the week ending July 5 there were 84 deaths in the City of New Orleans, 50 being in the white population and 34 in the nonwhite. Of these deaths six were in infants under one year of age; four white and two colored. The week which terminated July 12 showed an increase of 70 deaths; the unusual number of 106 occurring in the white population and 48 in the colored. An increase was also noted in the number of infant deaths, there being a total of 16 with ten of these occurring in the white race. There was a decrease of 40 deaths in the city during the week which ended July 19. Seventy-two white citizens and 42 colored expired this week. The number of infant deaths was the same as for the preceding week, however the majority of these occurred in the colored population; 11 colored and five white. The report for July 26 indicated 152 deaths which was considerably higher than the number for the week of July 19 and exceeded the three year median corresponding week by 21. This week the deaths were divided 86 and 66 between the white and colored respectively. The week of August 2 showed a drop in number of deaths over the previous week this year, however the number was over the three year median. There were 137 deaths reported; 92 white, 45 colored and 17 in children under one year of age.

INFECTIOUS DISEASE IN LOUISIANA

The weekly morbidity report for the State of Louisiana for the week ending July 5 showed pulmonary tuberculosis leading all other reported diseases. There were 45 cases of pulmonary tuberculosis listed followed by 25 of measles, and 14 of bacillary dysentery. No other diseases were re-

ported in numbers greater than ten. There were, however, four cases of poliomyelitis reported in Caddo Parish and two cases of meningococcus meningitis reported; one each from Pointe Coupee and Richland Parishes. Cancer led all reportable diseases for the week ending July 12 when there were 44 cases reported. Pulmonary tuberculosis followed with 34 cases and unclassified pneumonia with 22. Report of poliomyelitis cases decreased this week to one case from St. Landry Parish. Pulmonary tuberculosis and cancer still headed the lists of diseases reported for the week ending July 19. This week there were 39 of the former and 37 of the latter reported, and again, the only other disease reported in number greater than ten was unclassified pneumonia with 16 instances. One case of meningococcus meningitis was reported from St. Bernard Parish and one case of poliomyelitis from Caddo. The number of pulmonary tuberculosis cases decreased during the week ending July 26 to 12 cases, however cancer was still in the lead with 49 cases, followed by 33 of unclassified pneumonia, 15 of whooping cough and 12 of amebiases. Poliomyelitis was still in evidence in Caddo Parish where two additional cases were reported and another was reported in Calcasieu. Caddo Parish also reported one case of meningococcus meningitis and Ouachita Parish reported two cases of this disease.

MONTHLY MORBIDITY FOR VENEREAL DISEASES STATE OF LOUISIANA

Month Ending June 30, 1947

	Total This Month	Total Previous Months	Total to Date 1947
Chanchroid	49	280	328
Gonorrhea	1118	6279	7397
Granuloma Inguinale	23	82	105
Lymphopathia Venereum	3	38	41
Syphilis	860	4908	5768

FRANK BROSTROM

1894-1947

Dr. Frank Brostrom died suddenly in New Orleans on July 31. Dr. Brostrom was one of the well known group of orthopedic surgeons in New Orleans. He was connected with the staff of Touro Infirmary and the New Orleans Dispensary for Women and Children. He came to New Orleans some fifteen years ago, already well trained in his specialty. He had been with the Infantile Paralysis Foundation in Warm Springs, Georgia for a period of time and is said to have attended the late President Roosevelt. Dr. Brostrom was not only an outstanding man in his field but also was notable for the kind and splendid service he gave to his indigent patients.

Shortly after migrating to New Orleans Dr. Brostrom became a member of the State Medical Society. He was a graduate of Jefferson Medical College in Philadelphia.

BOOK REVIEWS

Occupational Diseases of the Skin: By Louis Schwartz, M. D., Louis Tulpian, M. D. and Samuel Pack, B. S., M. D. 2d ed. rev. Philadelphia, Lea & Febiger, 1947. Pp. 964, Illus. pl. Price, $12.50.

This is a thoroughly revised and improved text. It should be of especial interest to those practicing industrial medicine and surgery, employers in occupations presenting hazards to the employee, to the insurer and to those eligible or ineligible of employment. Compensation laws of the several states are described and an extensive bibliography are included.

Sensitivity to external irritants showing the influence of race, color, perspiration, diet, age, sex, season, cleanliness and either existing or previous dermatoses, are fully discussed.

Patch testing is outlined and its value after the development of a dermatitis venenata or its use before employment is stressed. Pages and pages of detailed descriptions of irritations, with their causes, methods of weeding out diseases or other causes and methods of approach are contained in this volume, the life's work of Dr. Louis Schwartz in his office as Industrial Surgeon of the U. S. Public Health Service with the able assistance of Drs. Tulpian and Pack. It is a volume of experience detailed to keep the employer and employee out of the law court and a necessary text for the interested physician.

M. T. VAN STUDDIFORD, M. D.

If You Need an Operation: By Richard A. Leonardo, M. D., Ch. M., F.I.C.S. New York, Froben Press, 1947. Pp. 198. Price, $3.00.

If one realizes the mental state that prospective surgical patients and their relatives go through, then the publication of this book fulfills a very necessary role—one might say it should be part of the preoperative treatment.

Confusing thoughts which naturally arise in the patient's mind are simply and lucidly classified.

The medical "language" used should not be beyond the grasp of the average patient (or their relatives mind you) and the author deals intelligently from the surgeon's and patient's points of

view, with the general outline of the object and procedure of the operation.

But, to certain types of patients, a little knowledge is a dangerous thing, and as the author deals with postoperative complications as well, such highly strung patients would do well not to read the book.

In general, however, it is felt that both patient and surgeon will greatly benefit from a perusal of this book.

DENIS ROSENBERG, M. D.

Diseases of the Skin, for Practitioners and Students: By George Clinton Andrews, A. B., M. D. 3d ed. Philadelphia, W. B. Saunders Co. 1946. Illus. Pp. 937. Price, $10.00.

This edition, like its predecessors is ideal for the student and practitioner. Emphasis has been placed on removing much of the old and obsolete material which was "carried over" from older authorities and a concise, condensed description of new discoveries has filled the space. This edition has a greater amount of printed matter due to a better utilization of the space on each page.

The Chapter on Symptomatology and General Diagnosis makes for a better understanding of the material in orderly form. Roentgen ray therapy, which is excellently described and radium therapy are brought up to date. Dermatitis venenata is enlarged upon and the role of focal infection is stressed in all the toxic manifestations of dermatoses. The use and misuse of the sulfones and antibiotics are fully discussed. The author has spared no effort in getting outside assistance for such subjects as fungous diseases, pathology of varisosities and occupational diseases. This edition is highly recommended for the ready-reference shelf of the medical profession.

M. T. VAN STUDDIFORD, M. D.

Muscle Testing, Techniques in Manual Examination: By Lucille Daniels, M. A., Marian Williams, M. A. and Catherine Worthingham, M. A. Philadelphia, W. B. Saunders Co., 1946. Pp. 189, illus. Price, $2.50.

This book presents a detailed yet simplified and coordinated approach towards manual muscle testing. It is a practical manual designed primarily for teaching the student to analyze and grade movement in terms of specific muscular action. The introduction briefly but adequately covers the origin and development of muscle testing in this country, and a helpful chart shows nine different methods of muscle testing which have been used by different individuals or groups.

The book deals with muscle groups of defined body areas, and emphasis has been placed on the testing of prime movers in relation to the principal joints of each segment of the body. The assimilation of valuable anatomic information concerning muscle insertions and origins, joint ranges, and nerve distribution with physiological data concerning prime movers, fixation of specific group action and synergistic action, along with clearly illustrated methods for testing neuromuscular conditions in a systematized order meets a definite need for students, physical therapists, and physicians and surgeons interested in the teaching and practice of orthopedic surgery and physical medicine.

Another outstanding feature is the abundance of clear and concise diagrammatic drawings which amply supplement the text.

The only undesirable feature is the lack of a more permanent binding.

R. M. KIMBALL, M. D.

Therapeutic Exercise: By F. H. Ewerhardt, M. D. and Gertrude Riddle, B. S., R. N., R. P. T. Philadelphia, Lea & Febiger, 1947. Pp. 152. Price, $2.50.

This book is concise manual designed for students of physical education, occupational therapy, and physical therapy. The material is presented in a didactic fashion with anatomic and physiologic consideration of joint movements and their analysis, particular emphasis having been placed on the musculature and nerve supply of the extremities.

The physiology and special application of therapeutic exercises are well presented with adequate space devoted to the indications and contraindications, as well as the specific exercises utilized in the treatment of weakness of the feet, abdomen, and the low back, and the preoperative management of scolosis.

The section on the teaching of posture, and the application of exercises in cardiac and respiratory disease, as well as other common conditions, should be of benefit to the general practitioner.

The section on poliomyelitis is concerned primarily with the Kenny Method during the acute phase and the methods of muscle function testing and muscle re-education during the latter phases, without, however, any reference to the use of braces.

The section on spastic paralysis is well balanced, and presents the current methods available for rehabilitation of the various types of this disorder.

The text suffers by the lack of illustrations, and the didactic approach necessary for conciseness, but it is a handy reference book for surgeons and physiotherapists who wish to give the patient a precise program of exercise, and it adequately fulfills its object as a teaching manual.

R. M. KIMBALL, M. D.

PUBLICATIONS RECEIVED

American Medical Association, Chicago: Annual Reprint of the Reports of the Council on Pharmacy and Chemistry of the American Medical Association for 1946.

McGraw-Hill Book Company, New York: The Years After Fifty, by Wingate M. Johnson, M. D.